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Metabolic disorders and gastroenteropancreatic-neuroendocrine tumors (GEP-NETs): How do they influence each other? An Italian Association of Medical Oncology (AIOM)/ Italian Association of Medical Diabetologists (AMD)/ Italian Society of Endocrinology (SIE)/ Italian Society of Pharmacology (SIF) multidisciplinary consensus position paper

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ABSTRACT

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogeneous group of malignancies derived from neuroendocrine cells that can occur anywhere along the gastrointestinal tract. GEP-NETs incidence has been steadily increasing over the past decades, in parallel with the increasing incidence of the metabolic syndrome (MetS). It is not yet fully known whether the MetS components (such as obesity, dyslipidemia and type 2 diabetes) could be involved in the etiology of GEP-NETs or could influence their outcomes.

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In this review, a panel of experts of the Italian Association of Medical Oncology (AIOM), Italian Association of Medical Diabetologists (AMD), Italian Society of Endocrinology (SIE), and Italian Society of Pharmacology (SIF) provides a critical view of the experimental and clinical evidence about the association of GEP-NETs risk, outcomes, and therapies with the metabolic disorders typical of MetS. The potential therapeutic strategies for an optimal management of patients with both GEP-NETs and MetS are also discussed.

1. Introduction

The World Health Organization (WHO) defines metabolic syndrome (MetS) as a pathologic condition characterized by abdominal obesity, impaired glucose regulation, hypertension, and hyperlipidemia (hypertriglyceridemia and low HDL-cholesterol), which increases the risk of developing type 2 diabetes (T2DM) and cardiovascular diseases (CVD) (Cornier et al., 2008; Eckel et al., 2010). During the years, MetS has been defined slightly differently by various scientific organizations (Table 1) (Alberti et al., 2009, 2005; Cleeman, 2001; Saklayen, 2018; WHO, 1999), however at present any definition is arbitrary.

The incidence of MetS often parallels the incidence of obesity and T2DM, which represent its major components. Obesity is currently one of the most widespread health threats, reaching epidemic proportions worldwide: in 2016, more than 1.9 billion of adults aged 18 years and over (39 % of the world population) were overweight and, of these, over 650 million (13 %) were obese. Worldwide obesity has nearly tripled since 1975, and its prevalence continues to grow both in adults and children. Over 4 million people die each year as a result of being overweight or obese (WHO, 2020). Obesity, however, is not always synonymous with MetS, since a significant percentage of the obese population is relatively metabolically healthy (insulin-sensitive, normotensive, and normolipidemic) (Saklayen, 2018). On the other hand, the number of people with diabetes has quadrupled in the past three decades, representing a major challenge for patients and healthcare systems. According to the International Diabetes Federation (IDF), approximately 463 million adults between the ages of 20–79 years (9.3 %) have diabetes, 90 % being T2DM. It was estimated that four million deaths globally in 2017 were caused by diabetes (Saeedi et al., 2019). Nevertheless, the presence of T2DM alone is not sufficient to determine the presence of MetS (Alberti et al., 2009, 2005; Cleeman, 2001).

Indeed, since MetS represents a cluster of abnormalities and its prevalence estimates vary based on the criteria used for its definition, global data about MetS spread is currently missing. In epidemiological studies, MetS occurrence varies between 20 % and 45 % of the general population, and it is expected to increase to approximately 53 % in 2035 (Engin, 2017; Gierach et al., 2014). Interestingly, it has been proposed that MetS is about three times more common than diabetes and therefore over a billion people in the world may be now suffering from this condition (Saklayen, 2018).

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogeneous group of malignancies derived from neuroendocrine cells that can occur anywhere along the gastrointestinal tract (Cives and Strosberg, 2018), most frequently in the stomach, pancreas, small intestine, colon, cecum, appendix and rectum (Dasari et al., 2017) (Fig. 1).

These neoplasms are characterized by the ability to produce, store, and secrete a large number of peptide hormones and biogenic amines which can lead to the development of distinct clinical syndromes. Based on this, GEP-NETs can be subdivided into "functional" or "non-functional" tumors, depending on the presence or the absence of a clinical syndrome attributable to hormonal hypersecretion (Cives and Strosberg, 2018). Intestinal NETs are hormonally functioning in 20 % of cases, and pancreatic NETs (pNETs) are functional in 10–30 % (Pavel et al., 2020). The hypersecreted hormone and the ability to generate a secretory syndrome is linked to the primary tumor site as well as to its potential distant metastasis. Of note, several metabolic disorders may occur during these hypersecretion syndromes.

GEP-NETs should be classified based on morphology and proliferation (and, rarely, mutation spectrum) into well-differentiated (WD) NETs (from grade1 [G1], more differentiated, to grade 3 [G3], less differentiated) and poorly-differentiated neuroendocrine carcinomas (NECs) (always G3) (Table 2) (Nagtegaal et al., 2020; Pavel et al., 2020).

GEP-NETs incidence has been steadily increasing over the past years (6.5-fold increase over the past four decades), representing the second most common gastrointestinal cancer. In the Surveillance, Epidemiology, and End Results (SEER) program (2000–2012), the reported annual incidence was 3.56 per 100,000 persons, accounting for 30 % in the small intestine, 30 % in the rectum, and 135% in the pancreas (Fig. 1) (Dasari et al., 2017). The growing incidence trend of GEP-NETs is most likely explained by the improved diagnostic accuracy and screening programs (Dasari et al., 2017; Lee et al., 2019). Likewise, the awareness of a correlation between GEP-NETs and metabolic disorders is increasingly emerging, opening a new biological and clinical landscape.

Interestingly, the increase in the incidence of GEP-NETs appears to parallel the increasing incidence of metabolic disorders, such as MetS. However, it is not yet fully known whether MetS could be involved in the etiology of GEP-NETs or could influence their outcomes. In this review, a panel of experts of the *Italian Association of Medical Oncology* (AIOM), *Italian Association of Medical Diabetologists* (AMD), *Italian Society of Endocrinology* (SIE), and *Italian Society of Pharmacology* (SIF) provides a critical view of the experimental and clinical evidence about the association of GEP-NETs and their therapies with metabolic disorders typical of MetS, with a specific focus on how good metabolic control, obtained through a nutritional intervention, lipid-lowering drugs, and/or anti-

Table 1
Most popular definitions of metabolic syndrome used for surveys and health care plans.

	WHO (WHO, 1999)	NCEP-ATP3 (Cleeman, 2001)	IDF (Alberti et al., 2005)	IDF & AHA/NHLBI (Alberti et al., 2009)
	High blood glucose along with any two or more of the following:	*Presence of any three or more of the following:*	*High waist along with the presence of two or more of the following:*	*Presence of any three or more of the following:*
Blood glucose (mg/dL)	> 110 2 h after glucose load > 140	> 100 or drug treatment	> 100 or diagnosed diabetes	> 100 or drug treatment
HDL cholesterol (mg/dL)	< 35 (*m*) or < 40 (*w*)	< 40 (*m*) or < 50 (*w*) or drug treatment	< 40 (*m*) or < 50 (*w*) or drug treatment	< 40 (*m*) or < 50 (*w*) or drug treatment
Triglycerides (mg/dL)	> 150	> 150 or drug treatment	> 150 or drug treatment	> 150 or drug treatment
Obesity				
Waist/hip ratio (cm)	> 0.9 (*m*) or > 0.85 (*w*)	–	–	
Waist (cm)	–	> 102 (*m*) or > 88 (*w*)	> 94 (*m*) or > 80 (*w*)	
BMI (Kg/m^2)	> 30	–	–	
Blood pressure (mmHg)	> 140/90	> 130/85 or drug treatment	> 130/85 or drug treatment	> 130/85 or drug treatment

m, men; w, women. BMI, body mass index; IDF, International Diabetes Federation; NCEP-ATP3, National Cholesterol Education Program – Third Adult Treatment Panel; WHO, World Health Organization.

diabetes drugs, can influence the outcome of GEP-NETs. The potential therapeutic approaches for optimal management of patients with both GEP-NETs and MetS are also addressed.

2. Metabolic derangements as risk factors for GEP-NETs

2.1. MetS

MetS components have been investigated as risk factors for several types of cancer. However, evidence concerning the role of MetS as a potential risk factor for NETs is still to be consolidated. Previous studies showed a significant association between MetS and a diagnosis of WD GEP-NETs (Santos et al., 2018), with higher risk for males and older patients (Santos et al., 2019). Single MetS components, such as increased waist circumference, elevated fasting triglyceride levels, impaired fasting plasma glucose (FPG) and insulin resistance (IR), were significantly more frequent among WD GEP-NET patients as compared with controls (Santos et al., 2018). In addition, MetS was found to be significantly associated with the presence of metastatic disease, suggesting that a poor metabolic health may be an important risk factor for WD GEP-NETs, similarly to what was reported for other malignancies. The same Authors described a significant association between MetS and G1 tumors (Santos et al., 2019), possibly suggesting that MetS might not induce tumor de-differentiation. On the other hand, a casual association cannot be ruled out, since MetS is very frequent among Caucasian subjects, and G1 NETs are more frequent as compared to higher-grade NETs. In a recent cross-sectional, case-control, observational study carried out on 109 patients with histologically confirmed G1/G2 GEP-NETs and 109 healthy subjects, patients with GEP-NETs had a higher MetS presence compared with controls (Barrea et al., 2021). In addition, the presence of MetS was more frequent in G2 than in G1 patients, in patients with progressive disease, and in metastatic vs non-metastatic patients, and was significantly correlated with the worst clinical severity of NETs (Barrea et al., 2021).

2.2. Obesity

Obesity is frequently associated with IR and consequent insulin overproduction. Insulin is a consolidated trigger for several signalling pathways involved in cell proliferation that may, in turn, influence tissue neoplastic transformation (Giovannucci et al., 2010). GEP-NETs, especially type 1 gastric carcinoids, that are rare in the general population, show a higher incidence in obese patients (Modlin et al., 2003). Type 1 gastric carcinoids are related to atrophic gastritis and G-cell hyperplasia, which has been demonstrated to follow hyperphagia and abnormal feeding behaviour in animal studies (Campos et al., 1990). The finding of type 1 gastric NETs in obese patients has been indeed previously reported (Al-Harbi et al., 2013; Csendes et al., 2007), supporting the hypothesis that obesity and abnormal feeding behaviour may be predisposing factors for type 1 gastric carcinoids. In addition, Barrea et al. (Barrea et al., 2018) showed that GEP-NET patients eat reduced amounts of unsaturated fats, plant protein and complex carbohydrates, and higher amounts of simple carbohydrates and polyunsaturated fatty acids, as compared to the general population, supporting the hypothesis that these patients may have an abnormal feeding behaviour. Therefore, a link between eating behaviour, overweight/obesity, and GEP-NETs development is not unlikely. However, the link could be different according to the site of NET development. Leoncini et al. (Leoncini et al., 2016), in a meta-analysis, showed that body mass index (BMI) may represent a risk factor for pNETs, but not for small intestinal and rectal NETs. Moreover, a previous study suggested a negative association between overweight/obesity and small bowel NETs (Hassan et al., 2008), while another study confirmed a positive association between obesity and pNETs (Valente et al., 2017). Therefore, the association between obesity and GEP-NETs needs further investigation, especially concerning site-specific differences.

Table 2
WHO 2019 classification for GEP-NETs (modified from (Nagtegaal et al., 2020)).

Morphology	Grade	Mitotic count (2 mm^2)[a]	Ki-67 index (%)[b]
Well-differentiated	G1	<2	<3
	G2	2–20	3–20
	G3	>2	>20
Poorly-differentiated (NECs)	G3	>20	>20

NECs, neuroendocrine carcinomas; *GEP-NETs*, gastroenteropancreatic neuroendocrine tumors. [a] 10 high-power field = 2 mm^2, at least 40 fields (at 40 magnification) evaluated in areas of highest mitotic density. [b] Percentage of tumor nuclei positive for the proliferation marker Ki-67 staining.

2.3. Dyslipidemia

Dyslipidemia has been listed among cancer risk factors based on the evidence that lower plasma total cholesterol is associated with a higher risk of cancer (Rose and Shipley, 1980). However, the evidence linking dyslipidemia and GEP-NETs is still very scant. A Korean cross-sectional study showed that low levels of HDL-cholesterol represent an

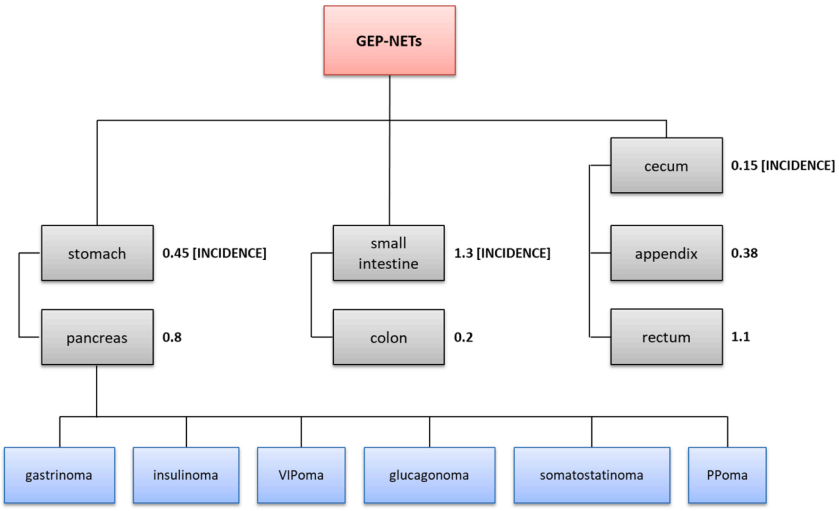

Fig. 1. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) most frequent localization and incidence. Age-adjusted incidence is calculated as number of new cases per 100,000 persons. Data are from the Surveillance, Epidemiology, and End Results (SEER) program and refer to the year 2012 (Dasari et al., 2017).

independent risk factor for rectal NETs (Jung et al., 2014). This finding was further confirmed by a recent study showing that patients with NECs had significantly lower total cholesterol and HDL-cholesterol levels as compared to the background population (Zou et al., 2021), but available data cannot identify lipid derangements as possible risk factors for GEP-NETs.

2.4. Diabetes

Diabetes mellitus (DM) has been reported as a risk factor for GEP-NETs. The exact mechanism is unknown, but some Authors hypothesized that the diabetes-associated chronic inflammation, in combination with hyperglycemia, could be responsible for oncogenic mutations and consequent tumor development through the activation of oxidative stress processes (Gallo et al., 2018).

In 2008, a case control study of 740 patients with GEP-NETs identified diabetes as a risk factor for gastric NETs and pNETs. However, a previous history of diabetes was only significant in women with gastric NETs, while in pNETs this relationship was only observed for diabetes that had been diagnosed within 1 year of NET diagnosis (Hassan et al., 2008).

Several case-control studies on the association between diabetes and pNETs have been published in the last years. In a study comprising 162 sporadic pNETs and 648 controls from two referral Italian centers, diabetes was identified among the risk factors independently associated with pNETs, together with high alcohol intake and history of pancreatitis (Capurso et al., 2009). Diabetes was then confirmed as a risk factor for pNETs in a large case-control study conducted in U.S. at the Mayo Clinic, while smoking, alcohol use, and family history of cancer were not significant (Halfdanarson et al., 2014). In a Chinese case-control study, diabetes was once again identified as an independent risk factor for pNET, but only for nonfunctioning types (Ben et al., 2016). Similarly, in the Chinese population, the prevalence of diabetes and new-onset diabetes in pNETs was reported to be 17.3 % and 8.6 %, respectively. The prevalence increased to 26 % in patients older than 60 years, resulting to be higher than the estimated rate of diabetes in the elderly Chinese population (Zhuge et al., 2020).

Importantly, in most studies, only the recently-onset diabetes (diagnosed within 12 months before the diagnosis of NET) was significantly associated with the risk of pNETs development (Ben et al., 2016; Capurso et al., 2009; Hassan et al., 2008). However, in a multicentric European case-control study, non-recent onset diabetes (>12 months before the diagnosis of pNETs) was more frequent in patients with sporadic pNET (n = 201) than in controls (n = 603) (OR = 2.09; 95 % CI, 1.27–3.46) and was associated with metastatic disease or advanced grade (G3) at the time of diagnosis (Valente et al., 2017). In general, in these studies, the different geographical origin of the studied populations and the different criteria used to define control subjects represent a limit in data interpretation. Overall, two recent meta-analyses concluded that history of diabetes was a significant risk factor for pNETs (OR = 2.74; 95 % CI, 1.62–4.62; P < 0.01) (Haugvik et al., 2015), and that both BMI and diabetes were relevant risk factors for gastric, pancreatic and small intestine tumors (OR = 2.76; 95 % CI, 1.65–4.64; P = 0.090) (Leoncini et al., 2016), regardless of study population and ethnicity. Unfortunately, only three studies were eligible for the meta-analyses concerning the relationship between diabetes and pNETs. Furthermore, these studies were highly heterogeneous due to study population and data collection.

3. GEP-NETs and their therapy can induce metabolic disorders

So far we have focused on how metabolic disorders can represent a risk factor for the development of GEP-NETs. Conversely, in this paragraph we will focus on how GEP-NETs, especially pNETs, can promote metabolic disorders, particularly diabetes, through different mechanisms.

The first link between GEP-NETs and the development of diabetes has a biological explanation. As already discussed, hormonal hypersecretion is typical of NETs and about one third of GEP-NETs is associated with a syndrome of hormone excess (Faggiano et al., 2012). When the hypersecreted hormone exerts an inhibitory effects on insulin secretion, as in the case of glucagonoma and somatostatinoma that involve pancreatic α-cells and the duodenum, the overall effect of the endocrine syndrome is to cause hyperglycemia and diabetes (Gallo et al., 2018).

In addition to biological causes, also surgery and anti-proliferative therapy, generally used for the management of these tumors, may induce impairment of glucose metabolism. Indeed, surgical treatment of pNETs usually consists of partial resection or tumor enucleation, as well as, more rarely, total pancreatectomy. Obviously, all these approaches cause reduction of the pancreatic β-cell functional mass and are associated with the onset or worsening of diabetes to varying degrees, especially in patients with hyperglycaemia and IR prior to surgery (Gallo et al., 2018).

Accordingly, in diabetic patients with newly diagnosed NETs (including GEP-NETs), although the mean HbA1c level did not change significantly during the course of cancer treatment, the use of insulin increased from 25 % at the time of cancer diagnosis to 35 % 1 year after cancer diagnosis, suggesting worsening of glycemic control and a need for therapy intensification (Kusne et al., 2021).

Hyperglycaemia and IR could also be promoted as adverse effects of the medical therapy of GEP-NETs. The first-line therapy for unresectable GEP-NETs includes somatostatin analogues (SSAs), which bind to somatostatin receptors (SSTRs) and exert anti-secretive and anti-proliferative effects. Octreotide and lanreotide (the first generation SSAs) mainly bind to SSTR2, reducing both insulin and glucagon secretion. In a minority of patients, the inhibition of insulin is higher than glucagon, thus causing hyperglycaemia. Interestingly, Umlauft et al. (Umlauft et al., 2017) showed no increased risk of developing DM after radiolabelled-octreotide therapy in patients with NETs. However, a higher prevalence of DM in patients before radiopeptide therapy was observed, probably due to a stringent diagnostic work-up coinciding with detection of NETs or exposure to therapies with diabetogenic potential before radiopeptide treatment (Umlauft et al., 2017). On the other hand, the pan-SSTR ligand pasireotide, which inhibits insulin secretion much more potently than glucagon due to its high affinity for SSTR5, induces hyperglycaemia in about 30 % of GEP-NET patients (Gallo et al., 2018). A well-defined second-line therapy for GEP-NETs is everolimus, a mammalian target of rapamycin (mTOR) inhibitor. This pathway plays a key role in regulating cell growth but also glucose metabolism. In GEP-NETs, everolimus is reported to induce glucose intolerance and diabetes in about 13 % of patients. Everolimus-induced hyperglycaemia could be due to both IR and decreased insulin secretion (Vergès and Cariou, 2015). In addition, dyslipidemia has also been reported as a consequence of treatment with everolimus. Indeed, mTOR inhibitors both reduce LDL receptor expression, inhibiting cholesterol endocytosis and causing an increase in total cholesterol serum levels (Sharpe and Brown, 2008), and increase the total free fatty acid pool as well as triglyceride levels (Brown et al., 2007). In clinical practice, treatment with mTOR inhibitors has been associated with a ~4.5-fold increase in the risk of serious metabolic adverse events, including hypertriglyceridemia and hypercholesterolemia (Sivendran et al., 2014). A retrospective study including 53 NETs (75 % pNETs) showed that everolimus treatment was associated with the development of grade 2 hypercholesterolemia in 23 % of the patients, requiring treatment with lipid-lowering drugs in a median time of 3.7 weeks. The occurrence of this side effect of everolimus was significantly associated with longer progression free survival (PFS), probably because the occurrence of hypercholesterolemia under everolimus treatment may be an early marker of response to treatment (Benslama et al., 2016). Dyslipidemia usually develops 2–4 weeks after treatment initiation and disappears 8 weeks after drug discontinuation, indicating that the abnormalities in lipid metabolism are reversible (Morviducci et al., 2018). Based on these

considerations, all patients planned to undergo treatment with everolimus should be screened for dyslipidemia before and during treatment, since progressive and severe hypertriglyceridemia and hypercholesterolemia may develop, requiring therapeutic adjustments or everolimus withdrawal.

In addition to targeted therapy, other anti-tumor agents used in NETs management could induce metabolic derangements (Silvestris et al., 2020). Indeed, interferon-α and streptozotocin, responsible respectively for β-cells autoimmune and cytotoxic damage, are known to induce hyperglycaemia, while chemotherapy, employed in the treatment of aggressive NETs, may also alter lipid profile by reducing HDL-cholesterol (Sharma et al., 2016).

4. Can metabolic control and therapies used in patients with metabolic disorders influence GEP-NETs progression, survival, and recurrence?

Metabolic reprogramming has recently emerged as a hallmark of cancer, with glucose, amino acid and lipid metabolism crucially contributing to tumor cell bioenergetics and biomass formation. A common feature of cancer cell metabolism is the ability to acquire necessary nutrients from a frequently nutrient-poor environment and utilize them to maintain viability and grow (Pavlova and Thompson, 2016). In this paragraph, we will review if metabolic control, achieved through a nutritional and/or pharmacological approach, is able to modulate GEP-NETs progression, survival, and recurrence.

4.1. Obesity and dyslipidemia

Lipids crucially contribute to cancer cell bioenergetics and anabolic functions (Vernieri et al., 2016). Most human cancers are able to both uptake triglyceride or other lipid molecules from the extracellular environment and synthesize fatty acids *de novo* (Vernieri et al., 2019). Given the ability of cancer cells to self-generate fatty acids, reducing plasmatic triglyceride and cholesterol levels with dietary or pharmacological interventions may not effectively target lipid metabolism in tumors (Vernieri et al., 2016). Nevertheless, triglyceride and cholesterol levels could affect the efficacy of anti-cancer drugs. Accordingly, Vernieri et al. (Vernieri et al., 2019) have shown that, in advanced pNET patients treated with everolimus (n = 58), the presence of high plasma triglyceride levels during the first 3 months of treatment increased the risk of disease progression. In addition, in formalin fixed, paraffin embedded tumor specimens, higher intratumor levels of Acetyl-CoA carboxylase 1 (ACC1), the limiting step enzyme in the fatty acid biosynthesis pathway, were associated with lower PFS in everolimus--treated patients with advanced pNETs (Vernieri et al., 2019). As a consequence, targeting systemic and intratumor lipid metabolism through dietary (i.e. lipid restriction) or pharmacological interventions (i.e. metformin, statins) could potentially improve everolimus efficacy in patients with advanced pNETs (Vernieri et al., 2019).

However, attention should be paid to dietary interventions, since, in patients with GEP-NETs, malnutrition has been associated with nearly 5-fold higher odds of mortality, while obesity decreased the rates of cancer-related mortality (the “obesity paradox”) (Glazer et al., 2014). A retrospective study recently found an association between good nutritional status, adherence to a Mediterranean-style diet, and aggressiveness of GEP-NETs in a selected cohort of adult patients (Barrea et al., 2018). To date, it is widely recognized that poor nutritional status and low body weight can have a negative impact on GEP-NETs outcomes and reduce therapy success (Artale et al., 2020; Gallo et al., 2019).

Regarding pharmacological interventions, multiple evidence has highlighted the potential beneficial effects of lipid-lowering drugs on GEP-NETs outcomes. In a retrospective analysis of 445 patients with advanced pNET treated with SSAs alone or plus everolimus, the use of metformin in diabetic patients was associated with longer PFS independently of plasma glucose levels (Pusceddu et al., 2018). The Authors suggested that metformin could improve everolimus efficacy by lowering plasma triglyceride and cholesterol levels (Wulffelé et al., 2004).

Statins are commonly used lipid-lowering drugs in patients with MetS and T2DM. Intriguingly, it has been demonstrated that simvastatin decreased survival rate and migration capacity, and increased apoptosis levels in BON-1 and QGP-1 cells, two human pancreatic pNET cell lines (Herrera-Martínez et al., 2019). Similarly, lovastatin was able to affect the viability of human midgut (GOT) and BON-1 cell lines, although concomitant use of everolimus did not show additive effects (Nölting et al., 2015). Finally, treatment of BON-1 and CM insulinoma cell lines with fluvastatin led to a dose-dependent reduction in cell growth of 70 % in BON and >90 % in CM cells (Höpfner et al., 2006). To the best of our knowledge, no studies have tested the effects of statins on GEP-NETs outcomes *in vivo*. Of note, these effects could be independent from the LDL-cholesterol lowering action of statins, while deriving from a direct antitumor mechanisms involving cell-cycle arrest, apoptosis induction, and decreased invasion or metastatic capacity (Herrera-Martínez et al., 2019).

4.2. Diabetes

Enhanced glucose uptake and utilization are the most frequent metabolic abnormalities in human malignancies and sustain unrestrained growth and proliferation of neoplastic cells (Vernieri et al., 2016). Accordingly, as discussed above, T2DM is associated with higher risk to develop GEP-NETs. Despite this evidence, little and contrasting data are available about the effects of glycemic control on long-term outcomes of GEP-NETs.

Pusceddu et al. (Pusceddu et al., 2018) found that glucose levels were not associated with PFS in patients, both with and without diabetes, with advanced pNETs treated with SSAs alone or plus everolimus. Surprisingly, PFS was significantly longer in patients with diabetes than without diabetes (HR for patients with vs without diabetes, 0.63; 95 % CI, 0.50−0.80; P = 0.0002). This association was dependent on diabetes treatment, since PFS of patients treated with metformin was significantly longer than for patients without diabetes or patients with diabetes receiving other treatments (Pusceddu et al., 2018). Importantly, the benefit associated with metformin was independent of the antitumor treatment. These results represent a relevant finding because they suggest that metformin use is associated with an improved prognosis in advanced pNET patients regardless of glycemia and insulinemia levels, highlighting a potentially direct anti-cancer effect of metformin. On the other hand, despite the evidence that insulin therapy could promote tumor growth, diabetic patients receiving insulin did not have reduced PFS in this study (Pusceddu et al., 2018).

Conversely, Sandini et al. (Sandini et al., 2020) showed that in patients undergoing pancreas resection for pNETs, preoperative dysglycemia (blood glucose ≥140 mg/dL and/or HbA1c ≥6.5 %) was associated with reduced overall survival and recurrence-free survival, together with more lymph-node involvement and metastatic disease, regardless of the presence of diabetes. Similarly, Gong et al. (Gong et al., 2020) found that high pre-operative FPG levels (>100 mg/dL) were significantly associated with poor overall survival and recurrence-free survival in resected patients with pNETs who had no pre-existing DM. Importantly, this study, unlike Sandini et al. (Sandini et al., 2020), excluded the influence of anti-diabetes medications and diabetic complications on pNET prognosis. In both studies, the presence of DM was not independently associated with pNET prognosis. Accordingly, de Mestier et al. (De Mestier et al., 2020) found that the post-operative occurrence or worsening of DM, rather than pre-operative DM, increased the risk of recurrence in resected patients affected by pNET, regardless of the amount of resected parenchyma. Importantly, the postoperative use of metformin tended to decrease the risk of recurrence (De Mestier et al., 2020). In addition, Kusne et al. (Kusne et al., 2021) found that DM did not adversely affect the survival of patients with

newly diagnosed NETs (including GEP-NETs). Furthermore, DM does not appear to increase the mortality of NETs patients undergoing receptor-targeted radiopeptide therapy (Umlauft et al., 2017). Conversely, Capurso et al. (Capurso et al., 2009) included DM among the risk factors that can negatively influence tumor progression and aggressiveness. Altogether, these findings suggest that normal glycemic levels may be associated with a more favorable prognosis of GEP-NETs.

Although the anti-cancer potential of metformin has long been recognized, limited information is currently available regarding its effects on NETs (Thakur et al., 2019). The therapeutic effects of metformin have been reported in patients with T2DM suffering from concurrent pNETs (Pusceddu et al., 2016). In particular, in 31 patients with advanced pancreatic well-differentiated tumors treated with everolimus and octreotide, the use of metformin was associated with prolonged PFS. In addition, the use of metformin has also a rationale in limiting treatment-emergent hyperglycemia, an adverse event frequently reported with everolimus and octreotide, which may lead to treatment discontinuation (Pusceddu et al., 2016). Of note, metformin offers potential synergistic activity with everolimus and SSAs in inhibiting the pro-carcinogenic PI3K/AKT/mTOR axis. At present, there are no completed clinical studies that investigated the effects of metformin in NETs other than pNETs. On the other hand, several preclinical studies demonstrated the ability of metformin to inhibit cellular viability of NET cells of different origins (i.e., BON-1, QGP-1, GOT, and human neuroendocrine primary cell cultures) (Pusceddu et al., 2018, 2016; Thakur et al., 2019; Vlotides et al., 2014; Yamana et al., 2020). Therefore, metformin may improve GEP-NETs outcomes and the efficacy of anti-cancer therapies, such as everolimus and SSAs, regardless of its effects on glucose and insulin levels.

Other anti-diabetes therapies could influence GEP-NETs outcomes. Specifically, Hu et al. (Hu et al., 2017) showed that the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin suppressed NF-κB activation and inflammatory cytokines expression in rat insulinoma cells, suggesting that sitagliptin may exert direct anti-inflammatory effects in islet β-cells and therefore represent a potential treatment to be investigated in insulinoma patients. On the other hand, the use of incretin-based therapies, both glucagon-like peptide-1 receptor agonists (GLP-1RAs) and DPP-4 inhibitors, has been associated with expansion of the exocrine and endocrine pancreatic compartments, the former being accompanied by increased proliferation and dysplasia and the latter by α-cell hyperplasia with the potential for evolution into NETs (Butler et al., 2013), even though these results have not been confirmed by other studies (Gokhale et al., 2014; Lo et al., 2018), including two recent meta-analyses (Dicembrini et al., 2020; Wang et al., 2018). For this reason, their use in pNET patients remains controversial.

5. Patients with concomitant metabolic disorders and GEP-NETs: How to treat them?

5.1. Nutritional intervention

Nutritional therapy is a fundamental component of the treatment of patients with MetS, representing an indispensable tool to achieve good control of various parameters, including glucose, lipids, and blood pressure levels. However, the nutritional status also plays a key role in oncologic patients undergoing cancer therapies. Malnutrition is one of the most common conditions in patients with cancer, being more common with several types of tumors, including GEP-NETs. As mentioned above, inadequate nutrition can have a negative impact on GEP-NETs outcomes and reduce therapy success. Therefore, the nutritional status of patients with GEP-NETs is of great importance and can be particularly difficult to manage when diabetes or metabolic diseases coexist. The assessment of nutritional status should be recommended within routine clinical practice in the evaluation of patients with GEP-NETs, in order to identify high-risk subjects with a more aggressive tumor who could benefit more from specific nutritional interventions (Barrea et al., 2018).

A low intake of rapidly absorbed carbohydrates together with higher amounts of lipids and proteins are generally recommended for cancer patients (Arends et al., 2017), even if no dedicated guidelines exist for patients with GEP-NETs. Arguably, however, a similar advice could be given to patients with GEP-NETs and diabetes, in order to reduce their CVD risk, when supposedly life-expectancy is long enough (Ragni et al., 2021).

A healthy balanced diet has an integral role in overall diabetes management (ADA, 2021). Every patient should receive medical nutrition therapy with the following goals: a) to attain individualized glycemic, blood pressure, and lipid goals; b) to achieve and maintain body weight goals; c) to delay or prevent diabetes complications; and d) to keep GEP-NETs symptoms controlled. According to the American Diabetes Association, meal planning should be individualized since there is not a "one-size-fits-all" eating pattern for individuals with diabetes, and this is even more true for people with special comorbidities like GEP-NETs. A variety of nutrient-dense, high-quality foods (i.e., whole grains, vegetables, fruits, legumes, low-fat dairy, lean meats, nuts, and seeds) in appropriate portion sizes should be emphasized, maintaining the pleasure of eating and addressing individual needs. In this setting, particular attention should be paid to avoiding foods and beverages that may trigger constipation, diarrhoea, and/or flushing in patients with GEP-NETs (Gallo et al., 2019) (see Table 3).

As a general approach, overweight and obese patients should attain a sustained reduction $\geq$5−7% of initial body weight through a 500−750 kcal/day energy deficit. Among healthful eating patterns, a Mediterranean-style diet rich in monounsaturated fats (predominantly from olive oil), fruits, vegetable, whole-grains, and fish may be considered to improve glucose metabolism, blood lipids, and lower CVD risk (Esposito et al., 2009). Recently, the ketogenic diet, a high-fat, low-carbohydrate diet with adequate amounts of protein, has also been hypothesized to be a promising approach for the management of several types of cancer, including GEP-NETs (Muscogiuri et al., 2020). Of note, all these hypotheses need to be tested in prospective clinical trials.

5.2. Dyslipidemia

A significant increase in total cholesterol and triglyceride levels is commonly observed in patients with GEP-NETs treated with everolimus. Therefore, the assessment of the lipid profile is of paramount importance in this setting, allowing a personalized nutritional and pharmaceutical

Table 3
Foods and beverages that may trigger diarrhea and/or flushing in patients with GEP-NETs (*i.e.*, carcinoid syndrome and VIPoma).

Foods	
	Milk and dairy products
Fatty meals	Fried, fatty, greasy foods
	Processed foods
	Cayenne or chili pepper
Spicy foods	Curry
	Mustard
	Aged, fermented cheese (Parmesan, Pecorino, Cheddar, Cottage, Swiss cheese, etc.)
	Smoked/salted fish and meat (sausages, corned beef, herring)
Amines high foods	Broad bean, soybean products, soy sauce
	Fermented-tofu, sauerkraut
	Nuts
	Some fruits (avocado, banana, pineapple, raspberries)
Other	Raw vegetables and tomatoes
Beverages	
Alcohol and fermented drinks (beer)	
Vinegar	
Coffee and caffeine-containing drinks	
Carbonates drinks (soda)	
Chocolate (large amounts)	

approach potentially reducing the increased CVD risk (De Gennaro Colonna et al., 2018; Lombard-Bohas et al., 2014).

Lifestyle intervention and weight loss (if indicated) should always be recommended, tailoring nutrition intervention according to each patient's medical condition. Patients with GEP-NETs and hyperlipidemia resistant to dietary intervention alone may benefit from treatment with lipid-lowering drugs, especially if at increased risk for CVD disease and if life-expectancy is not shorter than 1 year. CVD risk in cancer patients can be calculated according to the SCORE system (https://www.escardio.org/Education/Practice-Tools/CVDprevention-toolbox/SCORE-Risk-Charts) (Breccia et al., 2014; Busaidy et al., 2012).

As described above, an inhibitory effect of statins on NET-cell aggressiveness has been reported both *in vitro* and *in vivo*, suggesting a potential therapeutic role for these drugs in the treatment of patients with NETs (Herrera-Martínez et al., 2019; Nölting et al., 2015).

Caution must be taken when prescribing lipid-lowering agents, due to the risk of drug-drug interactions with some cancer drugs that are metabolized by the cytochrome P450 system (CYP), such as sunitinib and other tyrosine kinases inhibitors (Busaidy et al., 2012; Silvestris et al., 2020). Pravastatin and rosuvastatin should be preferred to other statins that may expose to the risk of competitive inhibition of CYP 3A4, as well as fenofibrate to other fibrates in case of hypertrygliceridemia (Wiggins et al., 2016). Ezetimibe (alone or as an add-on to statins) may represent a reasonable option when cholesterol is not adequately controlled (Breccia et al., 2014). Antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK9), such as evolocumab and alirocumab, are now available for the treatment of individuals with high levels of total and LDL cholesterol (e.g., patients with familial hypercholesterolemia). Lomitapide and mipomersen, two microsomal triglyceride transport protein (MTP) inhibitors, have been approved for the treatment of patients with homozygous familial hypercholesterolemia (Blom et al., 2019). More recently, a long-acting small-interfering RNA inhibiting the synthesis of PCSK9 in the liver (inclisiran) has been approved for patients with elevated levels of LDL cholesterol despite maximally tolerated statin therapy (Lamb, 2021; Preiss et al., 2020). Finally, bempedoic acid is a new class of non-statin LDL-lowering therapy that targets the cholesterol biosynthetic pathway in the liver by inhibiting ATP-citrate lyase (ACLY). Of note, it has been proved that ACLY expression and activity is aberrant in many types of tumors, and its pharmacological or genetic inhibition may significantly inhibit cancer cell proliferation and induce apoptosis (Granchi, 2018). For these reasons, ACLY inhibitors have recently attracted interest as promising anti-cancer agents (Granchi, 2018). However, to the best of our knowledge, scarce experience is available with these new drugs in cancer patients.

5.3. Diabetes

The appropriate therapeutic approach to diabetes treatment in patients with GEP-NETs should consider the underlying causes responsible for hyperglycemia (pre-existent diabetes, secondary diabetes due to pancreatic surgery, functioning syndromes, or use of specific anticancer drugs), nutritional issues, liver and renal function, as well as life-expectancy (Gallo et al., 2018; Ragni et al., 2021).

When glucose control is not achieved with lifestyle correction alone, metformin is the preferred initial pharmacologic agent for the treatment of T2DM also in patients with cancer, if tolerated and not contraindicated. Indeed, as discussed above, treatment with metformin has been suggested to delay or slow the progression of different tumors, including GEP-NETs, potentially favoring patients' survival (Herrera-Martínez et al., 2019; Pusceddu et al., 2018, 2016).

After failure of metformin monotherapy, or in case of metformin-induced worsening of gastrointestinal abnormalities, the choice of the pharmacologic agent should be individualized based both on patients' and drug features. Ideally, hyperglycemia should be addressed considering the underlying pathophysiological mechanisms. When diabetes is due to a functioning GEP-NET secreting counter-regulatory hormones (i.e., glucagon or somatostatin), anti-diabetes drugs tackling IR such as thiazolidinediones (pioglitazone) should be preferred, when hyperglycemia is mild and in the absence of heart failure and peripheral edema. Conversely, insulin therapy is the most suitable option for patients with severe hyperglycemia due to impaired insulin secretion (diabetes secondary to pancreatic surgery or induced by anticancer drugs). Sulphonylureas and meglitinides should be avoided, especially in patients with liver or renal failure. DPP-4 inhibitors are a good approach when tolerability and side effects are relevant issues, potentially exerting anti-inflammatory effects on GEP-NETs (Hu et al., 2017). A bit more controversial is the use of GLP-1RAs in patients with pNETs, due to their potential pro-proliferative properties (Butler et al., 2013) (see previous paragraph). Among patients with established atherosclerotic CVD or indicators of high risk, established kidney disease, or heart failure (including patients with valvular involvement from carcinoid disease), sodium-glucose co-transporter-2 (SGLT-2) inhibitors with demonstrated CVD benefit are recommended, if the patient is not prone to diabetic ketoacidosis (e.g., in diabetes secondary to pancreatectomy).

Potential gastrointestinal side effects of anti-diabetes drugs (such as metformin, acarbose, and GLP-1RAs) should also be taken into account, especially in patients already suffering from abdominal pain, nausea, vomiting, and diarrhea as a consequence of the GEP-NETs or of the treatment with SSAs (Silvestris et al., 2020).

6. Conclusions

MetS has long been associated with an increased risk of developing different types of cancer. Whether this is also true for the GEP-NETs has yet to be proved, since to date only few studies have shown a significant association between MetS and GEP-NETs (Santos et al., 2019, 2018), and it cannot be excluded that such association is casual. On the other hand, single components of MetS, such as obesity and diabetes, represent a recognized risk factor for site-specific GEP-NETs, in particular pNETs (Ben et al., 2016; Capurso et al., 2009; Halfdanarson et al., 2014; Haugvik et al., 2015; Leoncini et al., 2016; Valente et al., 2017). The mechanisms underlying this association could include IR-induced insulin overproduction and the consequent hyper-activation of cell proliferation pathways, (Giovannucci et al., 2010) as well as chronic inflammation typical of diabetes and obesity (Gallo et al., 2018) (Table 4).

Conversely, GEP-NETs could also promote metabolic disorders, particularly hyperglycemia, through different mechanisms. Indeed, the hypersecretion of hyperglycemic hormones (especially in the case of

Table 4
Mechanisms through which metabolic disorders and GEP-NETs influence each other.

Metabolic disorders → GEP-NETs	
Cause	***Effect***
Obesity → insulin resistance → insulin overproduction	Cell proliferation → neoplastic transformation
Diabetes → chronic inflammation → oxidative stress	Oncogenic mutation → tumor development
Hyperglycemia → glucose uptake and utilization	Unrestrained growth and proliferation of neoplastic cells
Hyperlipidemia	Contribution to cancer cell bioenergetics and anabolic functions
GEP-NETs → Metabolic disorders	
Cause	***Effect***
Hormonal hypersecretion (glucagon, somatostatin)	Hyperglycemia and diabetes
Surgical treatment of pNETs	Diabetes
Use of somatostatin analogues (pasireotide > octreotide and lanreotide)	Hyperglycemia and diabetes
Use of everolimus	Glucose intolerance, diabetes, and dyslipidemia

glucagonoma and somatostatinoma) (Gallo et al., 2018), the partial and total resection of the pancreas, and the use of anti-proliferative drugs with hyperglycemic effects (i.e., SSAs and everolimus), may be responsible for the onset or worsening of diabetes in patients with GEP-NETs. In addition, everolimus could also cause dyslipidemia (Morviducci et al., 2018) (Table 4).

In this scenario, several studies have shown that good metabolic control could reduce the aggressiveness and improve the outcomes of GEP-NETs patients, as well as increase the efficacy of anticancer therapies (De Mestier et al., 2020; Gong et al., 2020; Sandini et al., 2020; Vernieri et al., 2019). To achieve metabolic control, a Mediterranean-style nutritional interventions (Barrea et al., 2018; Esposito et al., 2009), the use of lipid-lowering drugs, especially statins (Herrera-Martínez et al., 2019; Höpfner et al., 2006; Nölting et al., 2015), and the use of metformin as anti-diabetes therapy (De Mestier et al., 2020; Pusceddu et al., 2018, 2016) should be highly considered as first-line therapies in patients with GEP-NETs and concomitant metabolic imbalances. Finally, both oncologist and endocrinologist should consider that the correction of metabolic abnormalities, such as hyperglycemia, malnutrition and excess body weight, may improve the prognosis of GEP-NETs

Data availability

Data will be made available on request.

Autohr contribution

Conception: AN, NS, FG. Design: AN, NS, FG. Supervision: GDB, SG, AR, MM, NS, FG. Data collection and/or processing: all Authors. Literature review: all Authors. Writer: AF, MCZ, AA, NM, SA, VA, PDB, RD, PF, SG, LM, ET, MM, MG.

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NS has served as consultant for Celgene and Isheo. GB has served as consultant for Roche, Servier, Celgene, Ipsen, Sanofi, Merck Serono. All other authors have declared no conflicts of interest.

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Lelio Morviducci, MD, PhD: Lelio Morviducci is full-time Director of the Diabetes and Nutrition Unit at Santo Spirito Hospital and San Filippo Neri Hospital –ASL Roma 1, Rome, Italy. He has been Visiting Research Fellow at the Diabetes Division of the University of Texas Health Science Center, San Antonio, directed by Prof. Ralph A. DeFronzo. Research interests are focused on diabetes, insulin resistance, diabetes technology and endocrine cancers. He is National Councilior of the Italian Association of Medical Diabetologists (AMD) and author of more than 100 peer-reviewed publications in scientific journals. He is reviewer of several national and international scientific journals.

Antonio Russo, MD: Antonio Russo, MD, is Full Professor of Medical Oncology at University of Palermo Medical School, Department of Surgical, Oncological and Oral Sciences (Italy). From 2004 to July 2011, he has been an Adjunct Associate Professor and since August 2011 Adjunct Full Professor at Temple University's College of Science and Technology, Philadelphia (USA). Since February 2012 is Director of Medical Oncology Unit and Director of Regional Reference Center for Prevention, Diagnosis and Treatment of Rare Tumors and Heredo-familial Solid Tumors in Adults, AOUP "P. Giaccone", Palermo (Italy). Since April 2012 to March 2019 and He has been, from April 2012 to March 2019 and from November 2021 to this day, he has been Director of the Specialization School in Medical Oncology, University of Palermo, School of Medicine, Palermo, Italy. Since April 2019 he is Coordinator of the PhD in Experimental Oncology and Surgery at University of Palermo, Department of Surgical, Oncological and Oral Sciences. Since November 2013 Medical Oncology Unit directed by Prof. A Russo has been recognized as a 2013 ESMO Designated Centres of Integrated Oncology and Palliative Care. Since 2001 he has been a coordinator with Prof D. Kerr (University of Oxford, UK) and Prof B. Iacopetta (Western Australia University) of the "CRCP53 International Collaborative Study". Since 2003 he has been an expert member of INSERM (Institut National de la Santè et de la Recherche Mèdical, France), since 2007 of Scientific Committee INCA (Institut National du Cancer, France) and of NWCRF (North West Cancer Research Fund, UK). He is member of Editorial board of Journal of Carcinogenesis & Mutagenesis and World Journal of Gastrointestinal Oncology and World Journal of Clinical Oncology. He is Associate Editor of Journal of Solid Tumors. Since 2008 he has been Guest Editor of Annals of Oncology (2006, 2007). The central theme of his studies is translational research, meaning the application of molecular genetics in cancer management. He is PI in several national and international clinical trials. He is the author of more than 300 peer-reviewed publications listed on Medline-PubMed.

Enzo Tuveri, MD: Enzo Tuveri is full-time MD at the Diabetology, Endocrinology and Metabolic Disease service of the hospital Santa Barbara in Iglesias, ATS Sardegna, Italy. He graduated in medicine and surgery in 2001 at the University of Cagliari and specialized in Endocrinology and Metabolic Disease in 2006 at the same University. He has been performing routine clinical and medical activities in the area of diabetes and diabetic foot. His clinical and research experience include type 1 and type 2 diabetes, use of technologies in patients affected by diabetes, gestationale diabetes and diabetic foot.

Monica Montagnani, MD, PhD: Associate Professor of Pharmacology at the Department of Biomedical Sciences and Human Oncology, Medical School, University of Bari Aldo Moro. Long-standing research interests are focused on diabetes, insulin resistance and vascular complication, cellular and molecular signaling of endocrine mediators in endothelium. Consultant for Diabetes Unit at the National Institutes of Health (NIH-US) and European Certified Pharmacologist (EuCP). Member of Pharmacology and Hypertension Scientific Societies, and editorial board member in International Journals. Invited speaker and Chairman at National and International congresses; co-author of over 80 scientific publications indexed in PubMed and Scopus (h-index 30, more than 6300 citations).

Marco Gallo, MD: Marco Gallo is Head of the Endocrinology and Metabolic Diseases Unit at the "Santi Antonio e Biagio e Cesare Arrigo Hospital" (Alessandria, Italy). Previously, he worked as senior specialist in the Oncological Endocrinology Unit at the AOU Città della Salute e della Scienza Hospital of Turin (2005–2020). He received his MD degree in 1992 from the University of Turin (Italy), and his Post Doctoral Specialization in Endocrinology and Metabolic Diseases in 1999 from the same University. His research interest include diabetes, treatment personalization of diabetes, diabetes and cancer, hormones and cancer, and endocrine cancers. He is author or co-author of more than 150 original papers and reviews (>70 indexed in PubMed) in peer-reviewed scientific journals. He is editorial board member in scientific journals as well as reviewer for many international scientific journals. He has also been a speaker at about 250 national and international conferences. He is member of AMD (Italian Association of Clinical Diabetologists), AME (Italian Association of Clinical Endocrinologists), and SIE (Italian Society of Endocrinology).

Nicola Silvestris, MD, PhD: Professor Nicola Silvestris is an Associate Professor of Medical Oncology at the University of Bari (Italy). He lends his teaching, research and assistance activities at the Department of Internal Medicine and Medical Oncology (DIMO) of the Faculty of Medicine of Bari and at the Cancer Institute "Giovanni Paolo II" of Bari. He was a Scientific Director of the Cancer Center of Bari until June 2019. He is a National Councilior of the Italian Association of Medical Oncology (AIOM). He is an author of over 210 publications in scientific journals with an impact factor. Over the past 15 years he has dedicated a large part of his research and assistance to patients suffering from gastrointestinal malignancies, with particular regard to hepato-biliary-pancreatic tumors. He has also been a speaker at over 300 national and international conferences.

Francesco Giorgino, MD, PhD: Professor Francesco Giorgino is Full Professor of Endocrinology, Chairman of the Department of Emergency and Organ Transplantation, and Head of the Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, at University of Bari Aldo Moro, Bari, Italy. He received his MD degree from the University of Bari Aldo Moro and his PhD degree from the University of Naples Federico II, in Italy. After completing clinical and research training in endocrinology and metabolism at the University of Catania, Italy, he worked for several years at the Joslin Diabetes Center and Harvard Medical School in Boston, MA, USA, first as a postdoctoral research fellow and then as a visiting scientist. Professor Giorgino has received distinguished scientific awards from various international and national institutions, including the Juvenile Diabetes Research Foundation International (JDRF) Fellowship (New York, NY, USA), the Mary K. Iacocca Foundation Fellowship (Boston, MA, USA), the Glaxo-Wellcome Award from the European Association for the Study of Diabetes (EASD), the Aldo Pinchera and Cassano Awards from the Italian Society of Endocrinology, and the Alcmeone Award from the Italian Society of Diabetology. He has been the Italian Delegate in various European Commission Cooperation in Science and Technology (COST) actions for diabetes research. Professor Giorgino has served on many national commissions and national boards, including the Executive Committee of the Italian Society of Diabetology, and the Scientific Committee of the Italian Society of Endocrinology. He has been President of the Italian Society of Endocrinology (2019–2021). He is or has been a member of the Editorial Boards for numerous. He has published more than 250 original and review articles in prestigious scientific journals (H-index of 53, over 9000 citations) and has been an invited speaker at many national and international meetings. He is named inventor in an approved Italian patent titled "Pharmacological use of a myokine able to preserve the function and mass oh the pancreatic cells under dysmetabolic conditions". Professor Giorgino's research interests include the mechanisms of insulin resistance and beta-cell dysfunction in type 2 diabetes mellitus, the pathophysiology of adipose tissue, and the pharmacological modulation of insulin action and beta-cell function.