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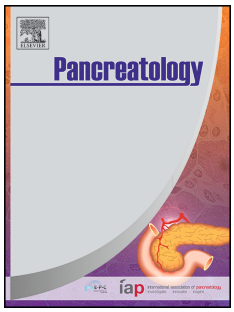


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# Occurrence of Exocrine Pancreatic Insufficiency in Patients with Advanced Neuroendocrine Tumors Treated with Somatostatin Analogs

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**Short title**: EPI in NEN patients treated with somatostatin analogs.

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**Abstract**

**Background**. Although exocrine pancreatic insufficiency (EPI) has been described in patients with neuroendocrine neoplasia (NEN) treated with somatostatin analogs (SSAs), its role in the therapeutic management of these patients is not well established. **Aim**. To determine the frequency of EPI in patients with NEN long-term treated with SSAs. **Methods**. This is a prospective single-center study evaluating 35 patients treated with SSAs for > 12 months due to unresectable/advanced nonpancreatic well-differentiated NEN. Clinical evaluation, biochemical parameters, and fecal elastases 1 (FE-1) were assessed to diagnose EPI. **Results**. A total of 7 patients (20%) had EPI, given the presence of abdominal symptoms and a median FE-1 value of 180 mcg/g stool (150 – 198). No patient had severe EPI, defined as FE-1 < 100 mcg/g stool. Elevated glycated Hb levels were a significant predictor for developing EPI (OR 4.81, p=0.01). No significant difference in terms of duration of SSA treatment was observed between patients with or without EPI diagnosed (84 months and 72 months, respectively; p=0.950). **Conclusions**. Mild-moderate EPI is a relatively common condition in patients receiving long-term treatment with SSAs. Specific clinical and biochemical evaluations, including FE-1, should be planned in these patients to diagnose this relevant condition early, which may deteriorate quality of life and cause malnutrition.

**Keywords** Neuroendocrine tumors; exocrine pancreatic insufficiency; somatostatin analog; malnutrition; pancreatic enzymes.

**Background**

Neuroendocrine neoplasia (NEN) is a heterogeneous tumor arising in secretory cells of the diffuse neuroendocrine system. These tumors are characterized by a relatively indolent rate of growth and the ability to secrete a variety of peptide hormones and biogenic amines (1).

In a series of 64,971 NENs reported by the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, their reported annual age-adjusted incidence rate grew from 1.09 per 100,000 in 1973 to 6.98 per 100,000 in 2012 (2).

Neuroendocrine neoplasias are considered heterogeneous diseases in terms of both clinical and pathological features, with a relatively indolent clinical course compared with nonendocrine malignancies. Their prognosis is affected by a number of factors, including primary tumor site, tumor grading (expressed by the Ki67 index), disease staging, and tumor burden (1, 3, 4).

Given their rarity and heterogeneity, the management of patients with NEN is still considered a clinical challenge, requiring dedicated multidisciplinary teams, including oncologists, endocrinologists, gastroenterologists, surgeons, pathologists, radiologists, and nuclear medicine physicians (5, 6).

A peculiar NEN feature is represented by the expression of somatostatin receptors (SSTRs) on the tumor cell surface, which are present in the vast majority of tumors. Somatostatin receptor expression, which can be assessed in vivo by performing 68Ga-DOTA-peptide positron emission tomography (PET) (68Ga-PET), is the basis for treating patients with NEN with somatostatin analogs (SSAs), which to date are widely considered the first-line therapeutic step for these patients (7).

Beyond their effect on symptoms due to functional syndromes, SSAs (octreotide long-acting release (LAR) 30 mg and lanreotide autogel 120 mg) have a clear effect on tumor proliferation in well-differentiated, slow-growing G1 and G2 NENs, as shown by two phase-3 trials (8,9).

The most frequently reported drug-related adverse events (AEs) are biliary disorders (including biliary stones in approximately ¼ of patients), gastrointestinal disorders (14 - 38%) and injection-site pain (20 - 50%). Hypoglycemia (4%), hyperglycemia (27%), sinus bradycardia (19%), conduction abnormalities (9%) and arrhythmias (3%) have also been reported (7, 10).

Exocrine pancreatic insufficiency (EPI) is a condition caused by secretion or reduced or inappropriate activity of pancreatic juice and its digestive enzymes. EPI can cause clinical manifestations such as steatorrhea, weight loss and biochemical changes related to malabsorption and maldigestion of lipids and fat-soluble micronutrients (11 - 13).

Due to the large reserve capacity of the pancreas, mild to moderate exocrine insufficiency can be compensated for, and steatorrhea symptoms may not be present unless pancreatic lipase secretion is reduced to <10% (severe/decompensated insufficiency). However, patients with compensated EPI still have an increased risk of nutritional deficiencies (in particular, of fat-soluble vitamins with related clinical consequences) (12).

Somatostatin analog treatment inhibits the production and excretion of pancreatic enzymes (14), and EPI is reported as a possible adverse effect of SSA treatment (15, 16). However, data on EPI in patients with NEN receiving SSAs for a long time are scant.

The aim of this study was to evaluate the occurrence of pancreatic exocrine insufficiency in a homogeneous group of patients affected by gastrointestinal (GI) NENs treated with somatostatin analogs for at least 12 months.

## Patients and methods

### *Patient selection*

This is a single-center prospective study conducted at the ENETS Center of Excellence of Rome – Sant'Andrea Hospital site from January to June 2019. A series of consecutive patients with the following inclusion criteria was enrolled: i. sporadic, histologically proven diagnosis of NET G1 or NET G2; ii. gastrointestinal origin of primary tumor; iii. advanced/unresectable disease; iv.

expression of somatostatin receptors as confirmed by positive 68-Gallium PET; v. active treatment with long-acting SSA for at least 12 months. Patients with pancreatic primary NEN were excluded.

Tumors were retrospectively classified according to the WHO 2019 classification (17) and staged according to the ENETS staging system (18) after revision of available histological slides and radiological images. Patients were defined as having a "functioning tumor" if typical carcinoid syndrome was present; otherwise, they were classified as "nonfunctioning". Patients in whom the primary tumor site was unknown were also included if they were believed to belong to the small bowel due to the presence of a carcinoid syndrome and confident histological criteria after other common primary sites had been ruled out by conventional imaging procedures (CT or MRI, as appropriate, and $^{68}$Ga-PET), as previously reported by other authors (19).

***Patient evaluation and follow-up***

The endpoint was to define the occurrence of EPI in patients treated with somatostatin analog long acting release for at least 12 months. Pancreatic exocrine insufficiency was diagnosed in the presence of clinical signs of malabsorption and/or maldigestion (steatorrhea, weight loss, flatulence, and abdominal distention) in addition to fecal elastase – 1 (FE-1) levels below 200 mcg/g stool. Severe EPI was considered in the presence of FE-1 values below 100 mcg/g stool (20-22).

In addition to FE-1, at time of the inclusion in the study, the following tests were assessed in all patients: vitamin D, parathormone, glycated hemoglobin, basal glycemia, serum calcium, total cholesterol and triglycerides.

The following values were considered normal references: vitamin D (low: <10 ng/m; insufficiency: 10 – 30 ng/mL; sufficient: 30 – 100 ng/mL); parathormone (10-65 pg/mL - 10-65 ng/L); glycated hemoglobin (<6%; 20 - 42 mmol/L); glycemia (70-99 mg/dL); serum calcium (8.9-10.1 mg/dl); total cholesterol (<239 mg/dl); and triglycerides (<150 mg/dl).

Pancreatic enzymatic replacement therapy (PERT) was given, when requested, at a standard dose of 40-50,000 Ph.U. with main meals and half that dose with snacks, as recommended (22, 23).

The study was approved by the local ethics committee and informed consent for data collection was obtained from all patients.

***Statistical Analysis***

The distribution of continuous variables is reported as medians and ranges. The Wilcoxon test was used to compare continuous variables, whereas Fisher's exact test and chi-square tests were used to compare different subgroups, as appropriate. Risk factor analysis was performed using a logistic regression model. All variables with significant results by univariate analysis were included in the multivariate model, which was constructed by the stepwise method. Differences were considered significant when the p value was $< 0.05$. Statistical analysis was performed using dedicated software (MedCalc, www.medcalc.org).

**Results**

Among the 125 NEN patients visiting the Sant'Andrea Hospital site of Rome (part of the Rome ENETS Center of Excellence) during the study period, 35 patients fulfilled the inclusion criteria and were enrolled in this prospective study. The patients' general features are summarized in Table 1.

In the vast majority of patients (n = 31, 88.5%), the primary tumor was located in the ileum, whereas in the remaining 4 patients (11.5%), the primary tumor was detected in other gastrointestinal sites (duodenum, n=2; right colon, n=1; stomach, n=1).

As far as the WHO 2019 classification is concerned, 21 patients (60%) had a NET G1, and 14 (40%) had a NET G2. The median Ki-67 proliferative index was 2% (range 1% - 20%).

A total of 26 patients (75.3%) had a nonfunctioning tumor, whereas the remaining 9 patients (25.7%) had a tumor-related carcinoid syndrome and were thus classified as "functioning tumor". Six patients (17.1%) had diabetes diagnosed before the inclusion in the study. As far as treatment is concerned, 31 patients (88.6%) were receiving standard doses of SSAs (octreotide LAR 30 mg/4 weeks in 21 patients, lanreotide autogel 120 mg/4 weeks in 10 patients). In the remaining 4 patients

(11.4%), the standard doses of SSAs were administered at shorter intervals (every 3 weeks) to achieve optimal control of tumor-related carcinoid syndrome.

The median duration of SSA treatment before the study inclusion was 84 months (range 12-204 months).

All patients were treated with somatostatin analog therapy due to advanced/unresectable disease. Specifically, 26 patients (74.2%) had liver metastases (stage IV disease), and 9 patients (25.8%) had lymph node metastases (stage III disease). Four patients (11.4%) also had distant extra-hepatic metastases (bone, n=3; lung, n=1). A total of 10 patients (28.6%) had progressive disease at time of the study inclusion, confirmed by radiological examinations (CT or MRI).

Primary tumor surgery had been performed in 23 patients (65.7%, all patients with small bowel NEN). In addition, 3 patients (8.5%) had received hepatic resection to remove synchronous liver metastases.

***Exocrine pancreatic insufficiency during SSA treatment***

Overall, EPI was diagnosed in 7 patients (20%), with FE-1 below 200 mcg/g stool in these patients (Table 1). In this group, 1 patient had manifested steatorrhea, and 2 patients presented significant weight loss. The remaining 4 patients had less evident abdominal symptoms, including flatulence and abdominal distention. No patient had severe EPI, defined as FE-1 below 100 mcg/g stool.

No significant difference in terms of duration of SSA treatment before the study inclusion was observed between patients with or without EPI diagnosed (84 months and 72 months, respectively; p=0.950) (Table 1).

No difference in terms of vitamin D levels, fasting glycemia, parathormone, total cholesterol or triglycerides was observed between patients with or without EPI. Conversely, higher glycated hemoglobin levels and lower serum calcium values were observed in patients with EPI compared with those without EPI (Table 1).

Abdominal symptoms improved in all patients in the EPI group after the initiation of replacement therapy with pancreatic enzymes, which were given at a standard dose of 40.000 Ph.U. with main

meals and half that dose with snacks in all patients with evidence of EPI, and further increased when appropriate according with clinical response.

***Predictors for exocrine pancreatic insufficiency***

When univariate analysis was performed to detect factors potentially related to increased risk for developing EPI, increased age at time of diagnosis, increased glycated hemoglobin value, and decreased calcium level were identified, with ORs of 1.10, 4.81, and 0.09, respectively (Table 2). However, after these variables were included in the multivariate model, only increased glycated hemoglobin values maintained statistically significant values (Table 2).

**Discussion**

In this prospective study, EPI was found in approximately 20% of patients with NEN receiving long-term treatment with SSA. No severe degree insufficiency was observed, since FE-1 levels were above 100 mcg/g stool in all patients.

In general, this finding is in agreement with previously reported data from other studies (15, 16, 24). However, EPI is an uncommon condition reported in patients treated with SSAs. In fact, this condition was rarely mentioned by both the phase-3 PROMID and CLARINET trials (8, 9), with EPI being reported in 0% and 5% of patients included in the active arm receiving octreotide or lanreotide, respectively. An explanation for this discrepancy may be found by analyzing different factors: i. EPI symptoms may overlap with other common adverse events related to SSAs, i.e., abdominal pain, flatulence, and diarrhea; ii. the length of SSA treatment may play a significant role: compared with this study, SSAs were used as first-line treatment in those RCTs, and the period of patient observation was quite short; and iii. including pancreatic NENs may further confound the interpretation of abdominal symptoms, since patients with large pancreatic lesions may develop pancreatic dysfunction due to the tumor itself. For these reasons, a direct comparison between this observational study and data drawn from phase-3 RCTs is not feasible.

In addition, the risk of potential low awareness of physicians prescribing SSAs should be considered. In general, EPI is an underestimated clinical condition (12) which may occur as a

consequence of different diseases, including pancreatic cancer (25, 26). In clinical practice, it may be difficult to diagnose, particularly in the early stages when patients are less symptomatic (25). It is thus reasonable considering this condition as undiagnosed in a significant proportion of patients with NEN receiving SSAs, in whom other more obvious causes of abdominal symptoms (advanced tumor disease, SSA common AEs, risk of previous abdominal surgery, possible concomitant medication with potential gastrointestinal toxicity) often coexist. Malnutrition resulting from EPI is a major effect of this disease and may be associated with serious consequences leading to increased morbidity, reduced survival, and deteriorated quality of life (26, 27). Malnutrition is commonly related to EPI and has been observed in a relevant proportion of patients with NEN (14%), suggesting a possible correlation with SSA treatment (28). Seeking EPI by using the noninvasive tool FE-1 is widely recognized as effective in the context of evaluating symptoms in patients with a high prevalence risk of pancreatic dysfunction, such as chronic pancreatitis and cystic fibrosis (21). Although presenting some limitations (i.e. difficulty to interpret moderately low levels and the low reliability for testing EPI in post-pancreatic resection) FE-1 may be considered the most widely available used diagnostic tool used to test for EPI in clinical practice (11-13). The present study suggests including this test in the laboratory evaluations that are scheduled in the follow-up of patients with NEN receiving SSAs, particularly when glycated Hb levels are above normal values, since these patients may be considered at risk for developing EPI. Unfortunately, the present study is unable to understand when EPI developed after SSAs initiation. Other studies reported that time to development of EPI ranged between 3 and 6 months (15, 16). Using the inclusion criteria of "long-term" SSAs treatment (> 12 months) to select patients as we did in the present study might result in missing early EPI diagnosis at the beginning of therapy. However, it contributed to make the population more homogeneous, and possibly reduced the risk to include patients with pre-existing pancreatic dysfunction not-related to SSAs administration. Although an elevated glycated Hb value was a significant risk factor for developing EPI ($p=0.01$ in multivariate analysis), caution should be used when analyzing this figure, since diabetes itself may be a cause of EPI due to a

complex relationship between the exocrine and endocrine pancreas (25). It is not possible to definitively understand whether increases glycated Hb levels were observed as a reflection of EPI or as a consequence of SSAs treatment which, as known, may induce worsening of serum glucose level control (29). Starting PERT in these patients may help understand the nature of abdominal symptoms and prevent worsening of malabsorption syndrome. The correct use of PERT remains a challenge for physicians dealing with EPI. In a recent survey on the appropriate use of PERT in patients with pancreatic cancer, it was observed that an appropriate prescription occurred in approximately 2/3 of patients, with 65% of them reporting compliance to therapy in terms of correct timing and modality of administration, confirming lack of awareness about PERT in the oncologist community (30). In the present study, all patients with diagnosed EPI received PERT, with subsequent improvement in abdominal symptoms, suggesting that they were related to pancreatic dysfunction instead of SSA AEs or syndromes related to functioning tumors. Unfortunately, the evaluation of symptomatic improvement was self-reported and not based on a specific QoL questionnaire. This is one of the weaknesses of the present study, which, although having the strength of prospectively analyzing a homogeneous series of patients with NEN, presents some limitations, i.e., the low number of enrolled patients, the lack of standardization of administered type/dose of SSA, and the wide range in the duration of SSA treatment before study initiation. However, some of these points may be ascribed to the rarity of NENs in general and to the difficulty of collecting data from selected homogeneous series of patients.

In conclusion, the present study shows that, although mild-moderate, EPI is a relatively common condition in patients with NENs receiving SSAs for a long time. Elevated glycated Hb levels were significantly associated with an increased risk of EPI. In these patients, routine FE-1 dosage should be planned in addition to the laboratory tests already scheduled during follow-up. Since EPI may cause abdominal symptoms overlapping with SSA-related adverse events, as well as specific syndromes related to the presence of functioning tumors, awareness about EPI diagnosis and treatment should be increased among the multidisciplinary community of physicians dealing with

NENs to increase QoL and improve the clinical outcome of these patients. Additional prospective clinical trials are needed to understand whether prophylactic PERT should be recommended in NEN patients treated with SSAs.

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Table 1. Patients' general features.

| | Overall (n=35) | EPI present (n=7) | EPI absent (n=28) | p |
|---|---|---|---|---|
| Median age (range) | 59 yr (42 – 84) | 70 yr (50 – 84) | 56 yr (42 – 81) | 0.020 |
| Performance status | | | | |
| ECOG 0 | 29 (82.8%) | 4 (57.1%) | 25 (89.3%) | 0.079 |
| ECOG 1 | 6 (17.1%) | 3 (42.9%) | 3 (10.7%) | |
| Grading | | | | |
| NET G1 | 21 (66.7%) | 3 (42.9%) | 18 (64.3% | 0.400 |
| NET G2 | 14 (23.3%) | 4 (57.1%) | 10 (35.7%) | |
| Functioning tumor | 9 (25.7%) | 2 (28.6%) | 7 (25%) | 0.622 |
| Diabetes before study inclusion | 6 (17.1%) | 2 (28.6%) | 4 (14.3%) | 0.576 |
| Duration of SSAs before study inclusion | 84 (12 – 204) | 84 (12 – 120) | 72 (12 – 204) | 0.950 |
| FE-1 value | 500 (150 – 500) | 180 (150 – 198) | 500 (263 – 500) | < 0.0001 |
| Fasting glycemia | 107 (78 – 217) | 135 (92 – 179) | 103 (78 – 217) | 0.094 |
| Glycated Hb | 6 (4 – 9) | 6.8 (5.8 – 9) | 5.8 (4 – 8) | 0.007 |
| Parathormone | 80 (25 – 236) | 93 (61 – 153) | 79 (25 – 236) | 0.332 |
| Vitamin D | 22 (3 – 50) | 14 (4 – 30) | 23 (3 – 50) | 0.154 |
| Calcium | 9.5 (6.9 – 10.5) | 9 (6.9 – 9.4) | 9.6 (8 – 10.5) | 0.003 |
| Cholesterol | 195 (89 – 277) | 195 (89 – 245) | 197 (100 – 277) | 0.577 |
| Triglycerides | 99 (45 – 822) | 85 (45 – 147) | 100 (53 – 822) | 0.364 |

EPI: exocrine pancreatic insufficiency; NET: neuroendocrine tumor; FE-1: fecal elastase-1

Table 2. Predictors for pancreatic exocrine insufficiency.

**Univariate analysis**

| *Variable* | *OR* | *95% CI* | *p* |
|---|---|---|---|
| Age*^ | 1.10 | 1.00 – 1.22 | 0.034 |
| ECOG 1 (vs ECOG 0) | 6.25 | 0.91 – 42.50 | 0.061 |
| Functioning tumor | 1.20 | 0.18 – 7.62 | 0.846 |
| Ki67* | 1.13 | 0.92 – 1.37 | 0.223 |
| Diabetes before study inclusion | 2.40 | 0.34 – 16.89 | 0.379 |
| Progressive vs stable disease§ | 2.25 | 0.40 – 12.61 | 0.356 |
| Extra-hepatic distant metastases | 1.38 | 0.12 – 15.81 | 0.791 |
| Duration of SSAs before study inclusion * | 0.99 | 9.98 – 1.01 | 0.406 |
| Therapy with octreotide vs lanreotide | 0.74 | 0.13 – 3.99 | 0.727 |
| Fasting glycemia* | 1.01 | 0.99 – 1.04 | 0.162 |
| Glycated Hb* | 4.81 | 1.33 – 17.33 | 0.001 |
| Parathormone* | 1.00 | 0.98 – 1.02 | 0.612 |
| Vitamin D* | 0.94 | 0.86 – 1.02 | 0.133 |
| Calcium*^ | 0.09 | 0.01 – 0.73 | 0.002 |
| Cholesterol* | 0.99 | 0.97 – 1.01 | 0.512 |
| Triglycerides* | 0.99 | 0.96 – 1.01 | 0.249 |

**Multivariate analysis^**

| *Variable* | *OR* | *95% CI* | *p* |
|---|---|---|---|
| Glycated Hb* | 4.81 | 1.33 – 17.33 | 0.01 |

* Continuous variable. ^ Variables “age” and “calcium” were excluded from the model by the stepwise process due to loss of significance. § At time of the study enrollment.