Association between somatostatin analogues and diabetes mellitus in gastroenteropancreatic neuroendocrine tumor patients: A Surveillance, Epidemiology, and End Results-Medicare analysis of 5235 patients

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Abstract

Background: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are increasingly common malignancies and tend to have favorable long-term prognoses. Somatostatin analogues (SSA) are a first-line treatment for many NETs. Short-term experiments suggest an association between SSAs and hyperglycemia. However, it is unknown whether there is a relationship between SSAs and clinically significant hyperglycemia causing development of diabetes mellitus (DM), a chronic condition with significant morbidity and mortality.

Aim: In this study, we aimed to compare risk of developing DM in patients treated with SSA vs no SSA treatment.

Methods and Results: Using the Surveillance, Epidemiology, and End Results (SEER) database and linked Medicare claims (1991-2016), we identified patients age 65+ with no prior DM diagnosis and a GEP-NET in the stomach, small intestine, appendix, colon, rectum, or pancreas. We used χ2 tests to compare SSA-treated and SSA-untreated patients and multivariable Cox regression to assess risk factors for developing DM. Among 8464 GEP-NET patients, 5235 patients had no prior DM and were included for analysis. Of these, 784 (15%) patients received SSAs. In multivariable analysis, the hazard ratio of developing DM with SSA treatment was 1.19, which was not statistically significant (95% CI 0.95-1.49). Significant risk factors for DM included black race, Hispanic ethnicity, prior pancreatic surgery, prior chemotherapy, tumor size >2 cm, pancreas tumors, and higher Charlson scores.

Conclusion: DM was very common in GEP-NET patients, affecting 53% of our cohort. Despite prior studies suggesting an association between SSAs and hyperglycemia, our analysis found similar risk of DM in SSA-treated and SSA-untreated GEP-NET patients. Further studies are needed to better understand this relationship. As NET patients have increasingly prolonged survival, it is crucial to identify chronic conditions such as DM that these patients may be at elevated risk for.
1 | INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are an increasingly common group of malignancies, with diagnosis rates increasing by more than sixfold in the last four decades and continuing to rise.\textsuperscript{1,2} Even in patients who present with advanced stage tumors, the long-term prognosis is relatively favorable, with median survivals of 5 years or more.\textsuperscript{3,4} A common first-line treatment for NETs is a somatostatin analogue (SSA), such as octreotide or lanreotide. Given the often-prolonged duration of treatment with SSAs and long survival of patients with GEP-NETs, it is important to understand the potential long-term effects of these treatments.

Diabetes mellitus (DM) is a serious condition that has been reported in approximately 21.4\% of all individuals over age 65.\textsuperscript{5} DM is associated with significant complications and morbidity, decreased quality of life, and increased mortality.\textsuperscript{6-10}

SSAs have been shown to alter glucose homeostasis. In clinical trials of the octreotide acetate long-acting injection in NET patients, hyperglycemia was observed in 27\%.\textsuperscript{11} Additionally, in small studies in non-NET patients, intravenous or subcutaneous octreotide was found to be effective in treating sulfonylurea-induced hypoglycemia in the acute setting.\textsuperscript{12,13} thought to be via octreotide’s inhibition of insulin release from pancreatic beta cells. However, the effects of SSAs on glucose regulation are complex. While SSAs inhibit insulin and glucagon-like peptide 1 (GLP-1) secretion, which increases blood glucose; they also inhibit secretion of the counterregulatory hormones, growth hormone and glucagon, thereby reducing insulin resistance and blood glucose levels.\textsuperscript{14-16}

Though less common than instances of hyperglycemia, hypoglycemia was observed in 4\% of NET patients in the octreotide clinical trials.\textsuperscript{11}

In NET patients, small studies have suggested an association between GEP-NETs and metabolic syndrome\textsuperscript{17} and higher fasting glucose,\textsuperscript{18} but these initial studies showed no statistically significant difference in these measures in patients treated with SSAs. Overall, although hyperglycemia is more often suggested than hypoglycemia, the net effect of SSAs on glucose homeostasis in GEP-NET patients is not well-understood. Additionally, whether SSAs predict clinically significant and long-term hyperglycemia causing subsequent diabetes mellitus has not been studied.

Therefore, our primary aim in this retrospective study is to determine whether SSA treatment independently increases risk of developing DM in GEP-NET patients.

2 | METHODS

2.1 | Study population

The study was approved by the Icahn School of Medicine Institutional Review Board: Study IRB-20-03072.
no DM diagnosis by the date of last follow-up were treated as censored observations. Kaplan–Meier survival analysis was performed to compare survival in DM patients vs non-DM patients, for the entire cohort of NET patients, and for subgroups of pancreatic primary tumors compared to tumors of other primary sites. A P-value of <.05 was considered statistically significant. All statistical analyses were performed using SAS (Cary, North Carolina).

3 | RESULTS

We identified 8464 patients with a pathologically confirmed GEP-NET from the SEER database and linked Medicare claims from 1991 to 2016. Of these, 3229 (38% of all GEP-NET patients) had a diagnosis of DM predating their NET diagnosis and were excluded from the main analysis. The remaining 5235 patients were included for analysis.
Of these patients, the vast majority never received SSA, with only 784 (15%) receiving SSA treatment after NET diagnosis. The median age of this cohort was 72, with even distributions of men and women (49.4% men). The large majority of patients (77.1%) were non-Hispanic white, 10.5% were non-Hispanic black, 5.4% were Hispanic, and 5.5% were Asian and Pacific Islander (API). Small intestine tumors were most common, making up 35.6% of all tumors included, followed by rectal (18.3%), pancreatic (17.4%), colonic (14.8%), gastric (9.7%), and appendiceal (4.3%) tumors. Tumor stage was bimodal, with a high frequency of stage 1 (40.4%) and stage 4 (33.1%) tumors, and just 9.8% stage 2 and 16.7% stage 3 tumors. Over half (55.3%) of tumors were grade 1 (well-differentiated), while 16.8% were grade 2 (moderately differentiated), and 27.9% were grade 3 (undifferentiated or poorly differentiated).

| Table 2: Characteristics of GEP-NET patients, by development of diabetes mellitus during study period |
|---------------------------------------------------------------|
| **Variable** | **No diabetes mellitus** | **Developed diabetes mellitus** | **P-value** |
| | N= 3916 | N= 1319 |  |
| **Age** | | |  |
| 65-69 | 1496 (38.2%) | 583 (44.2%) | <.0001 |
| 70-74 | 913 (23.3%) | 314 (23.8%) |  |
| 75-79 | 675 (17.2%) | 223 (16.9%) |  |
| 80+ | 832 (21.3%) | 199 (15.1%) |  |
| **Gender** | | |  |
| Male | 1965 (50.2%) | 623 (47.2%) | 0.06 |
| **Race/ethnicity** | | |  |
| Non-Hispanic white | 3092 (79.0%) | 946 (71.7%) | <.0001 |
| Non-Hispanic black | 373 (9.5%) | 179 (13.6%) |  |
| Hispanic | 192 (4.9%) | 88 (6.6%) |  |
| Asian/Pacific Islander | 204 (5.2%) | 82 (6.2%) |  |
| **Tumor size** | | |  |
| <1 cm | 612 (15.6%) | 204 (15.5%) | .57 |
| 1-2 cm | 745 (19.0%) | 251 (19.0%) |  |
| >2 cm | 1294 (33.0%) | 413 (31.3%) |  |
| Unknown | 1265 (32.3%) | 451 (34.2%) |  |
| **Stage** | | |  |
| I | 1369 (37.4%) | 589 (49.4%) | <.0001 |
| II | 343 (9.4%) | 133 (11.2%) |  |
| III | 623 (17.0%) | 189 (15.9%) |  |
| IV | 1325 (36.2%) | 281 (23.6%) |  |
| **Histological grade** | | |  |
| Well differentiated | 1022 (26.1%) | 314 (23.8%) | <.0001 |
| Moderately differentiated | 323 (8.3%) | 83 (6.3%) |  |
| Poorly differentiated and undifferentiated | 584 (14.9%) | 89 (6.8%) |  |
| Unknown | 1987 (50.7%) | 833 (63.2%) |  |
| **Primary site** | | |  |
| Appendix | 185 (4.7%) | 39 (3.0%) | <.0001 |
| Colon | 632 (16.1%) | 143 (10.8%) |  |
| Pancreas | 660 (16.9%) | 252 (19.1%) |  |
| Rectum | 662 (16.9%) | 294 (22.3%) |  |
| Stomach | 373 (9.5%) | 132 (10.0%) |  |
| Small intestine | 1404 (35.9%) | 459 (34.8%) |  |
| **Prior pancreatic surgery** | | |  |
| | 179 (4.6%) | 124 (9.4%) | <.0001 |
| **Carcinoid syndrome** | | |  |
| | 727 (18.6%) | 250 (19.0%) | .75 |
| **Prior chemotherapy** | | |  |
| | 593 (15.1%) | 232 (17.6%) | .04 |
| **Prior radiotherapy** | | |  |
| | 238 (6.1%) | 80 (6.1%) | .99 |
| **Modified Charlson comorbidity index** | | |  |
| 0 | 2232 (57.0%) | 778 (59.0%) | .21 |
| 1-2 | 893 (22.8%) | 266 (20.2%) |  |
| >3 | 161 (4.1%) | 62 (4.7%) |  |
| Unknown | 630 (16.1%) | 213 (16.2%) |  |
| **Received SSA** | | |  |
| | 544 (13.9%) | 240 (18.2%) | .0002 |
In an unadjusted comparison, 30.6% of patients who received SSA developed DM after NET diagnosis, vs 24.2% of patients who did not receive SSA ($P = .0002$) (Table 1). Patients who received SSA were significantly more likely to be younger (age 65-69 group), have received chemotherapy or prior radiation therapy, have clinical symptoms of carcinoid syndrome, and have a larger and later stage tumor. There were also statistically significant differences in the distributions of tumor site, race/ethnicity, and Charlson comorbidity score between groups that did and did not receive SSA.

Compared to those who did not develop DM, individuals who developed DM were more likely to have received SSA, chemotherapy, or pancreatic surgery. There were also statistically significant differences in age, race/ethnicity, stage, grade, and primary site distributions (Table 2). Additionally, in a univariate Cox regression model,

| Table 3: Risk factors for developing diabetes mellitus in multivariable analysis |
|-----------------------------|-----------------------------|-----------------------------|
| Variable                      | Hazard ratio | 95% confidence interval | P-value |
| Age                           |              |                           |         |
| 65-69                         | 0.89         | (0.77, 1.04)              | .14     |
| 70-74                         | 0.95         | (0.80, 1.12)              | .53     |
| 75-79                         | 0.85         | (0.71, 1.02)              | .08     |
| 80+                           | 0.96         | (0.85, 1.08)              | .46     |
| Gender                        |              |                           |         |
| Male                          | 1.19         | (0.97, 1.46)              | .09     |
| Race/ethnicity                |              |                           |         |
| Non-Hispanic white            | 1.58         | (1.33,1.89)               | <.0001  |
| Non-Hispanic black            | 1.58         | (1.25,2.01)               | .0002   |
| Hispanic                      | 1.21         | (0.95,1.54)               | .13     |
| Asian/Pacific Islander        | 1.15         | (0.73,1.80)               | .54     |
| Tumor size                    |              |                           |         |
| <1 cm                         | 1.19         | (0.97, 1.46)              | .09     |
| 1-2 cm                        | 1.35         | (1.09, 1.66)              | .005    |
| >2 cm                         | 1.15         | (0.96, 1.38)              | .13     |
| Stage                         |              |                           |         |
| I                             | 1.03         | (0.99, 1.33)              | .07     |
| II                            | 0.93         | (0.75, 1.15)              | .49     |
| III                           | 0.84         | (0.69, 1.02)              | .08     |
| IV                            | 0.85         | (0.70, 1.03)              | .09     |
| Histological grade            |              |                           |         |
| Well differentiated           | 1.01         | (0.77, 1.33)              | .92     |
| Moderately differentiated     | 0.97         | (0.75, 1.24)              | .78     |
| Poorly differentiated and undifferentiated | 1.15 | (0.99, 1.33) | .07 |
| Primary site                  |              |                           |         |
| Rectum                        | 0.94         | (0.74, 1.20)              | .62     |
| Colon                         | 1.49         | (1.16, 1.90)              | .002    |
| Pancreas                      | 1.49         | (1.16, 1.90)              | .0027   |
| Small intestine               | 0.92         | (0.76, 1.12)              | .41     |
| Stomach                       | 1.03         | (0.81, 1.30)              | .84     |
| Appendix                      | 0.79         | (0.55, 1.12)              | .18     |
| Prior pancreatic surgery      | 1.35         | (1.03, 1.75)              | .03     |
| Carcinoid syndrome            | 1.02         | (0.88, 1.20)              | .76     |
| Prior chemotherapy            | 1.25         | (1.06,1.49)               | .01     |
| Prior radiotherapy            | 1.12         | (0.88, 1.43)              | .36     |
| Modified Charlson comorbidity index | 0 | 1.19 | (0.95, 1.49) | .13 |
| 1-2                           | 1.24         | (1.07, 1.44)              | .0054   |
| 3 or greater                  | 2.40         | (1.80, 3.19)              | <.0001  |
| Unknown                       | 0.92         | (0.77, 1.09)              | .33     |

**Bold values indicates the statistically significant $P$-values.**
treatment with SSA with time-dependent adjustments showed a hazard ratio (HR) of 1.31 for developing DM, which was statistically significant (95% CI 1.09-1.58, \( P = .004 \)).

However, in a multivariable model with analysis of SSA with adjustment for other covariates, SSA-treated patients had similar risk of DM as SSA-untreated patients (HR 1.19; 95% CI 0.95-1.49) (Table 3). Patient factors associated with increased DM risk included Hispanic ethnicity (HR 1.58; 95% CI 1.25-2.01) and black race (HR 1.58; 95% CI 1.33-1.89). Age was not independently associated with development of DM. A sub-analysis excluding pancreatic tumors showed consistent results, with no significant difference in DM risk in SSA-treated and SSA-untreated individuals (HR 1.14; 95% CI 0.87-1.49).

Tumor factors associated with increased DM risk were primary pancreas tumors (HR 1.49, 95% CI 1.16-1.90) and tumors larger than 2 cm (HR 1.35, 95% CI 1.09-1.66). Tumor stage was not associated with development of DM. Likewise, clinical carcinoid syndrome was not significantly associated with the development of DM.

Overall survival in all individuals with GEP-NET was plotted with Kaplan–Meier analysis (Supplementary Figures). In Kaplan–Meier analysis comparing individuals with and without DM, survival in these groups was comparable (Figure 1). However, survival of individuals with pancreatic tumors was significantly less favorable than those with tumors of other primary sites (Supplementary Figures).

### DISCUSSION

Individuals with GEP-NETs are often treated with SSAs as a first-line treatment and stay on SSAs for a prolonged period, up to 10 years or more. It is therefore important to understand the long-term effects of SSAs. Some known potential risks of SSAs include exocrine pancreatic insufficiency (described in 20%-25% of patients) and biliary stone disease (described in 27% of patients treated with SSA). The effects of SSA on pancreatic endocrine function and glycemic control have not yet been elucidated, however, and are especially crucial to explore, given over half of all GEP-NET patients in our cohort (53%) developed diabetes mellitus in their lifetimes. Although our adjusted analysis demonstrates SSA treatment did not confer increased risk of DM in this cohort, our results show an overall much higher rate of DM in individuals with GEP-NETs compared to the general US population, in which 21.4% of adults over age 65 are diagnosed with DM.

To our knowledge, the relationship between SSAs and development of DM has not been studied in NET patients. The limited existing literature has shown mixed results on the relationship between SSAs and blood glucose levels. A number of studies in individuals without NETs and animal models have linked SSAs and hyperglycemia. These studies demonstrated that SSA administration results in increased blood glucose and suppressed insulin in rats, and increased blood glucose after sulfonylurea-induced hypoglycemia in humans. However, clinical trials for octreotide have reported instances of either hyper- or hypoglycemia in different individuals. Still others have reported no significant glucose alterations or only transient changes.
This is the first study to describe a markedly higher prevalence of DM in individuals with GEP-NETs compared to the general population over age 65. One group has previously observed an association between well-differentiated GEP-NETs and metabolic syndrome and visceral obesity.17,18 Higher fasting glucose and glucose intolerance were described previously in two small samples of patients with NETs; however, the prevalence of DM diagnoses in the GEP-NET population has not been studied.17,25 It has been proposed that DM and neuroendocrine tumors share components in their pathogenesis, though the exact mechanism is not known.26 This is supported by studies showing that some medications for diabetes such as metformin have been associated with slower tumor progression in NET patients.27,28 Further studies are needed to better explain these relationships.

We found significantly increased risk of diabetes in non-Hispanic black and Hispanic populations, which is consistent with prior data in both the general population and the elderly.29-31 A variety of socioeconomic (eg, neighborhood, income) and biologic (eg, BMI, waist circumference) risk factors have been linked to the higher rates of DM in these groups and are likely also at play in our patient population.32-34 Our findings that pancreatic NETs in particular predicted higher risk of DM has also been described previously, though the direction of causality has been unclear.35

Strengths of this study include the examination of an understudied patient population with GEP-NETs, a large sample size, and low rate of loss to follow-up. To our knowledge, there have been no prior studies of the relationship between use of SSAs and development of DM in individuals with GEP-NETs. Limitations of the study include the possibility of selection bias. Only patients over 65 and therefore eligible for Medicare were included, and this older sample may not represent all individuals with GEP-NETs. However, this study’s older population is an important population to understand, in light of prolonged survival of patients with GEP-NETs, as well as the aging of the US population as a whole. Additionally, the rate of SSA treatment was 15% of our sample, lower than expected given the largely well-differentiated and late-stage disease in this sample, which would likely be good candidates for treatment. This raises the possibility that SSA treatment data may be incompletely captured or underestimated in the SEER-Medicare database, or may represent differences in treatment practices over time. Low SSA treatment rates were similarly seen in a prior SEER-Medicare analysis of all nonpancreatic GI NET patients, in which just 6% of patients received SSA.4

Overall, our study shows a substantially higher rate of DM in individuals with GEP-NETs than in the general population. As patients with GEP-NETs have increasingly favorable cancer-related survival, it is important for clinicians to understand these patients’ increased risk of DM, given the significant morbidity and mortality of DM over time. Though some prior literature suggests SSAs are linked to hyperglycemia and glucose dysregulation, SSAs were not associated with increased risk of DM in our sample. Further studies are needed to better understand the relationship between glucose regulation, SSA treatment, and the increased DM risk in individuals with GEP-NETs.

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AUTHOR CONTRIBUTIONS
Katherine Ni: Conceptualization; data curation; formal analysis; investigation; methodology; software; visualisation; writing-original draft; writing-review and editing. Jeong Yun Yang: Data curation; formal analysis; methodology; software; writing-review and editing. Kiwoon Baeg: Data curation; formal analysis; methodology; software; writing-review and editing. Amanda Leiter: Methodology; validation; writing-review and editing. Grace Mhango: Data curation; methodology; software; writing-review and editing. Emily Gallagher: Conceptualization; validation; writing-review and editing. Juan Wisnivesky: Conceptualization; formal analysis; methodology; software; supervision; validation; writing-review and editing. Michelle Kim: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; validation; writing-review and editing.

CONFLICT OF INTEREST
Author J.W. received consulting honorarium from Sanofi, Banook, and GSK, and a research grant from Sanofi. Author E.G. has an advisory role for Novartis and consulting role for Seattle Genetics. The other authors declare no potential conflicts of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the CMS Information Management Services and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from https://healthcaredelivery.cancer.gov/seermedicare/ with the permission.

ETHICS STATEMENT
This study was approved by the Icahn School of Medicine Institutional Review Board: Study IRB-20-03072. This study has been done in accordance with the Publishing Ethics Guidelines outlined by the Committee on Publication Ethics (COPE).

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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