Cancer Treatment Reviews 67 (2018) 1–9

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

General and Supportive Care

Diabetes and pancreatic neuroendocrine tumours: Which interplays, if any?

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ARTICLE INFO

Keywords:
Neuroendocrine tumours
Diabetes
Nutrition
Lifestyle
Therapy

ABSTRACT

Pancreatic neuroendocrine tumours (PanNETs) represent an uncommon type of pancreatic neoplasm, whose incidence is increasing worldwide. As per exocrine pancreatic cancer, a relationship seems to exist between PanNETs and glycaemic alterations. Diabetes mellitus (DM) or impaired glucose tolerance often occurs in PanNET patients as a consequence of hormonal hypersecretion by the tumour, specifically affecting glucose metabolism, or due to tumour mass effects. On the other hand, pre-existing DM may represent a risk factor for developing PanNETs and is likely to worsen the prognosis of such patients. Moreover, the surgical and/or pharmacological treatment of the tumour itself may impair glucose tolerance, as well as antidiabetic therapies may impact tumour behaviour and patients outcome. Differently from exocrine pancreatic tumours, few data are available for PanNETs as yet on this issue. In the present review, the bidirectional association between glycaemic disorders and PanNETs has been extensively examined, since the co-existence of both diseases in the same individual represents a further challenge for the clinical management of PanNETs.

Introduction

Neuroendocrine tumours (NETs) constitute a heterogeneous group of neoplasms that can be associated with a broad range of local and systemic symptoms, related to tumour mass effects and/or to the secretion of several hormones, peptides, and biogenic amines [59,38]. They can arise almost anywhere in the body, even if the majority of NETs originate in the gastroenteropancreatic (GEP) tract or in the bronchopulmonary system (about 70% and 25% of NETs, respectively) [19]. The majority of NETs are sporadic, whereas 5–30% of cases can arise in complex hereditary endocrine disorders [23,24]. They can appear at all ages, but the highest incidence of sporadic GEP NETs is from the fifth decade onward [63].

Pancreatic NETs (PanNETs), accounting for 4–7% of GEP NETs [28], are sometimes associated with impaired glucose metabolism and/or to overt diabetes mellitus, which may result from a direct tumour effect on the pancreas, from the release of substances interfering with insulin secretion and/or activity, or from the surgical and/or medical treatment of the tumour itself. Furthermore, the increased life expectancy of patients with NETs has increased the number of subjects developing health conditions typical of the elderly, such as diabetes and its complications [35].

Beyond sharing some specific features (average age of onset, ongoing increase of incidence and prevalence, and probably some risk factors), the co-existence of a PanNET and diabetes mellitus (DM) in the same patient poses some complex clinical questions, such as: the metabolic effects of NETs therapies; the potential effects of some antidiabetic therapies on the neuroendocrine system; which antidiabetic therapy to use; the prognostic effect of diabetes on the tumour, and so on. This manuscript aims to review published data on the risk factors for PanNETs, to describe the consequences of NETs therapies on glucose metabolism, and to address some of the more common challenges of DM treatment in patients with PanNETs.

Epidemiology of PanNETs and diabetes

Although initially considered rare tumours, the incidence of NETs has gradually increased from 1.9 to 6.9/100,000 people per year during the last three decades, probably due to improvements in diagnostic techniques and increased attention from both clinicians and

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[1] Details of the NIKE Group is given in the Acknowledgement section.

https://doi.org/10.1016/j.ctrv.2018.04.013
Received 17 December 2017; Received in revised form 15 April 2018; Accepted 17 April 2018

Table 1
Estimated incidence of pancreatic neuroendocrine tumours according to cancer registries.[a]

panNET	Estimated incidence(per 1,000,000 people per year)
Non-functioning	4–5
Insulinoma	2–4
Gastrinoma	0.5–4
Glucagonoma	0.05
VIPoma, somatostatinoma, others	< 0.025

[a] Oberg and Eriksson [62], Dasari et al. [19].

pathologists [89,19]. The crude incidence of sporadic NETs increases with age, and it peaks between 50 and 70 years, except for the carcinoid of the appendix, occurring earlier in the majority of cases. A slight overall higher incidence of NETs was observed for males (5.35) compared with females (4.76) [63]. Nowadays GEP NETs represent the second most common gastrointestinal neoplasm after colorectal adenocarcinoma [91]. It should also be noted that the prevalence of GEP NETs in autopsy series is significantly higher than that observed in clinical series.

In Western countries, the estimated clinical incidence of PanNETs is approximately 0.8/100,000 people [19], albeit PanNETs have been described in 0.5%-1.5% of autopsies. Altogether, PanNETs account for only 1–2% of pancreatic neoplasms [62,52,19]. However, a sharp increase in the incidence of nonfunctioning PanNETs was described over the past decades, greater than 3-fold increase [28,52,19]. Indeed most of PanNETs are nonfunctioning, with surgical and medical series suggesting insulinoma and gastrinoma as the most common functioning forms (Table 1). Due to the relative indolent clinical course of PanNETs (relative to that of exocrine pancreatic carcinoma), to improvements in treatment strategies, and to the long survival of many patients, PanNETs prevalence is also increasing having been estimated to account for approximately 10% of all pancreatic tumours despite the lower incidence [28,91,19].

Conversely, diabetes mellitus (DM) is one of the main challenges of the 21st-century regarding global health. Despite relevant improvements in DM management, and declines in its rate of complications and mortality, the absolute numbers of people with DM is steadily increasing all over the world, with an unprecedented rise in low- and middle-income countries [61]. According to estimates from the International Diabetes Federation (IDF), there were 415 million people with DM in 2015, whereas the absolute number will reach 642 million by 2040 [44]. The IDF also estimates that by 2035 low- and middle-income countries will experience a 50% increase in the prevalence of impaired glucose tolerance (IGT, a form of prediabetes), compared with 41% increase in high income countries. It should be noted that, while the definition of DM and IGT is the same for the World Health Organization (WHO), the IDF, and the American Diabetes Association (ADA), impaired fasting glucose (IFG, the other condition of prediabetes) is defined as fasting plasma glucose level of 100–125 mg/dL (5.6–6.9 mmol/mol) according to the ADA definition, whereas as 110–125 mg/dL (6.1–6.9 mmol/mol) according to the WHO/IDF definition. Therefore, the ADA IFG definition recognizes more subjects at increased risk of developing DM (and with significantly increased cardiovascular risk) compared with the WHO/IDF definition [27]. Furthermore, among people with DM impressive improvements in outcomes occurred in Western countries over the past two decades. As a consequence, the absolute number of people with DM is constantly increasing [61].

Diabetes as a risk factor for PanNETs

The pathogenesis and the risk factors for sporadic PanNETs are not well defined, since little epidemiologic research in this area has been performed. According to the small number of available studies, a family history of any cancer (and of PanNETs in particular), DM, and perhaps a high BMI, have all been suggested as risk factors for PanNETs [40,13,97].

The association between DM and PanNETs has been examined by several case-control studies [39,13,39,6] and by two meta-analyses [41,53], which consistently indicated DM as a potential risk factor for the development of PanNETs. Leoncini and coll., in their recent systematic review and meta-analysis, reported a strong significant association between a history of DM and PanNETs, with a summary effect estimate of 2.76 (95% CI 1.65–4.64) [53]. This effect was even higher when considering subjects with non-functioning PanNETs [6] and those with “recent onset DM” (ie, DM diagnosed in the 12 months before the diagnosis of a PanNET) (OR 12.80, 95% CI 2.47–66.42). Together with gastric NETs, those of pancreatic origin are the GEP NETs where DM seems to represent the strongest risk factor.

It should be noted that obesity and DM have also been strongly associated with pancreatic ductal adenocarcinoma (PDAC), which is far more common than PanNETs, suggesting that NETs and adenocarcinomas might share some of the same risk factors, at least for this anatomical site [41,53]. Unfortunately, most of the studies considered in the meta-analysis did not provide data adjusted for important modifiable determinants of cancer risk such as diet, nutrition, physical activity, and the type of diabetes treatment.

The mechanisms linking DM to PanNETs development are largely unknown. The presence of the MEN-1 syndrome and the co-existence of a functioning PanNET may rise blood glucose levels, but it is a quite rare condition. Moreover, PanNETs may induce hyperglycaemia and peripheral insulin resistance by producing diabetogenic factors, similarly to advanced PDAC [75,77]. Therefore, DM can be an early paraneoplastic condition or a consequence of a tumour-induced impairment of glucose metabolism, instead of a real factor promoting cancer initiation (“reverse causality”) [16,64]. Alternatively, DM may act as a mediator for chronic inflammation and intracellular oxidative stress, leading to DNA mutation and to the development of PanNETs [6]. In addition, the progressive tumoural disease may cause the obstruction of the pancreatic duct and the disruption of vasculature, promoting the destruction or atrophy of pancreatic tissue, ultimately worsening insulin secretion [77]. Existing evidence suggests that reverse causality is unlikely to be entirely responsible for the observed association between DM and PDAC, whereas little evidence is available for PanNETs [47]. Further research is necessary to clarify this issue.

Mechanisms of diabetes onset in patients with PanNETs

Direct effect of functioning PanNETs

In patients with PanNETs imbalance of glucose metabolism and DM may be due to an altered secretion of hormones that can induce hyperglycaemia and insulin resistance, such as with glucagonomas or somatostatinomas, or to decreased insulin secretion, as it is the case of patients who underwent pancreatic surgery [72].

Glucagononoma

Glucagonoma is an uncommon tumour arising from pancreatic neuroendocrine islet α-cells secreting abundant glucagon. The estimated annual incidence of glucagonoma is ~1 case per 20,000,000 individuals [17]. Mortality rates remain unclear, with fewer than 300 cases reported and the largest case series including only 21 patients. The typical clinical presentation of glucagonoma usually manifests when these tumours are over 4–5 cm in size and metastatic, particularly to the liver. Glucagon exerts its physiological role by increasing the hepatic glucose output and maintaining normal blood glucose level. Furthermore, glucagon exerts a catabolic role by reducing protein synthesis. Therefore, elevated glucagon levels result in amino acid catabolism and serum glucose elevation, which are considered to be responsible of the typical skin lesions and DM.