

Case and Review

Mesenteric Variceal Haemorrhage and Ectopic Cushing's Syndrome as Presenting Features of a Pancreatic Neuroendocrine Tumour Recurrence

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Keywords

Cushing's syndrome · Ectopic varices · Gastrointestinal bleeding · Neuroendocrine carcinoma · Pancreatic cancer · Portal hypertension

Abstract

Pancreatic neuroendocrine tumours can have varied and complex presentations. Whilst hormone hypersecretion often induces characteristic clinical syndromes, non-specific symptoms may arise due to localized tumour effects. Malignant invasion of local vasculature is an increasingly recognized complication of these neoplasms and can be associated with significant morbidity. Herein, we present the case of a 47-year-old male with a recurrence of a pancreatic neuroendocrine tumour who presented with unusual upper gastrointestinal bleeding. The tumour had recurred within the superior mesenteric vein, replacing the vessel and invading its branches. This resulted in porto-mesenteric hypertension and the formation of bleeding mesenteric varices. The patient subsequently developed progressive metabolic disturbances and was diagnosed with ectopic Cushing's syndrome, despite his primary tumour having been non-functional. This case demonstrates not only a rare pattern of tumour recurrence but also the potential for pancreatic neuroendocrine tumours to de-differentiate and change from non-functional to hormone secreting, a phenomenon which may complicate diagnosis and management.

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Learning Points

- pNETs are more likely to cause tumour thrombosis or direct venous wall invasion than previously thought. This should be suspected in pNETs abutting vascular structures.
- Tumour thrombosis or direct venous wall invasion can lead to porto-mesenteric hypertension and upper gastrointestinal bleeding, at times from ectopic varices.
- Clinical syndromes caused by hormone release from a functional pNET may occur with localized, non-metastatic disease, and presenting features can be insidious.
- pNETs can be dynamic, and their functional status may change with recurrence.

Background

Pancreatic neuroendocrine tumours (pNETs) are rare, comprising 1–3% of all pancreatic malignancies [1, 2]. Though less common than lung or gastrointestinal neuroendocrine tumours [3], they are often of interest to clinicians due to their ability to induce unusual clinical syndromes. These occur following the pathological release of certain hormones including insulin, gastrin, glucagon, vasoactive intestinal peptide, and somatostatin [3, 4] and more rarely non-pancreatic peptides such as adrenocorticotrophic hormone (ACTH) [4]. Such secretory pNETs are classified as functional neoplasms; however, these only occur in around 10% of cases with the majority of all pNETs being non-functional [5]. Whilst non-functioning pNETs often still release various monoamines or peptides, these substances do not cause an established hormonal syndrome. These tumours instead present with non-specific symptoms related to tumour mass effect, commonly abdominal pain or jaundice [2, 4]. Upper gastrointestinal (UGI) haemorrhage has been associated with both functional and non-functional pNETs; however, this is usually in the context of well-recognized complications, such as gastric metastases [4] or Zollinger-Ellison syndrome [6].

Cushing's syndrome is a multi-system disorder caused by glucocorticoid excess. Ectopic ACTH secretion is an uncommon cause of Cushing's syndrome, responsible for <8% of all cases of endogenous hypercortisolaemia [7]. Often it results in fulminant disease though some ectopic ACTH tumours can remain undetected for many years [7]. Patients with ectopic Cushing's syndrome are more susceptible to infections and develop pronounced metabolic derangements including alkalosis and hypokalaemia [8]. Although most strongly associated with lung malignancies, pNETs have been implicated in up to 16% of cases of ectopic Cushing's syndrome [9].

Herein, we present an unusual case of UGI bleeding secondary to invasion of the superior mesenteric vein (SMV) by an intraluminal recurrence of a pNET. This resulted in porto-mesenteric hypertension and the formation of bleeding mesenteric varices, a phenomenon that to the best of our knowledge has not been previously documented in relation to a pNET. A subsequent diagnosis of ectopic Cushing's syndrome was also made; this was an unexpected finding as the primary tumour had been non-functional.

Case Presentation

A 47-year-old male presented to a UK teaching hospital with a 1-week history of melaena, passing 2 dark, tarry stools per day. He had also experienced 7 months of proximal muscle weakness associated with 12 kg of weight loss, equating to approximately 13% loss of his total baseline weight. On presentation, he was using a walking stick to compensate for ongoing right hip pain following a low energy fall from a bicycle 6 weeks beforehand. Pre-morbidly, he had never had any issues with mobility and had been a keen cyclist and runner.

He had a medical history of a grade 1 pancreatic head neuroendocrine tumour, staged at T3N1M0 with a Ki-67 index of <2% on biopsy. The tumour was non-functional with measured serum chromogranin A (CgA), chromogranin B (CgB), and gut hormone levels all within the normal range (CgA 1.8 nmol/L [<6 nmol/L], CgB 1.5 nmol/L [<3 nmol/L], VIP 5 pmol/L [<30 pmol/L], somatostatin 52 pmol/L [<150 pmol/L], pancreatic polypeptide 28 pmol/L [<300 pmol/L], glucagon 21 pmol/L [<50 pmol/L], and gastrin 9 pmol/L [<40 pmol/L]). This was diagnosed and surgically managed 6 years prior with a curative pylorus-preserving pancreaticoduodenectomy. His medication history therefore included pancreatin and a basal-bolus insulin regime of insulin glargine at night and insulin aspart with meals. He did not take any anticoagulant, antiplatelet, or non-steroidal anti-inflammatory medications. He was a non-smoker and consumed minimal alcohol, revealing no obvious precipitant for UGI bleeding.

On admission, the patient had a sinus tachycardia of 115 beats per minute with a blood pressure of 128/63 mm Hg. Physical examination revealed no peripheral stigmata of chronic liver disease; however, there was new bilateral pitting oedema to the mid-thigh. His abdomen was soft and non-tender to palpation with no appreciable hepatosplenomegaly. Digital rectal examination confirmed the presence of melaena.

Investigations and Diagnosis

Initial laboratory investigations revealed a haemoglobin of 85 g/L. This was an acute drop from a recent haemoglobin of 120 g/L which had been routinely checked by his general practitioner 10 days prior. His new anaemia was associated with a mildly raised urea of 8.3 mmol/L but normal creatinine of 77 µmol/L. He was also hypokalaemic at 2.9 mmol/L. All other routine tests were within normal reference ranges, including liver function (bilirubin 14 µmol/L, aspartate transaminase 28 IU/L, alkaline phosphatase 129 IU/L, and gamma-glutamyl transferase 23 IU/L), coagulation profile (international normalized ratio 0.93 and activated partial thromboplastin time ratio 0.85), and albumin (41 g/L). A 2D transthoracic echocardiogram showed no evidence of right- or left-sided cardiac dysfunction to explain his peripheral oedema. No source of bleeding was identified on 2 separate oesophago-gastro-duodenoscopies or on a colonoscopy. A video capsule endoscopy was also unremarkable.

A CT scan of the thorax, abdomen, and pelvis revealed evidence of portal hypertension with variceal dilatation of the superior and inferior mesenteric veins. There was no evidence of parenchymal liver disease, ascites, or pleural effusions. Sub-acute right pubic rami fractures were noted, attributable to his recent cycling accident. Subsequent gallium-68 DOTATATE positron emission tomography (PET) demonstrated avid uptake around the SMV confirming localized recurrence of the pNET (Fig. 1). These findings were initially interpreted as nodal recurrence within the mesenteric lymph node stations; however, re-review of his CT scan revealed that the tumour was in fact intraluminal, replacing the SMV trunk and invading multiple draining SMV branches (Fig. 2, 3). The resulting increased venous pressure had caused porto-mesenteric hypertension with the formation of bleeding mesenteric varices.

Management and Outcome

The patient was managed conservatively with blood transfusions and potassium replacement. He was commenced on a somatostatin analogue (lanreotide autogel 120 mg monthly) to inhibit tumour progression and was discharged 24 days after admission, following a prolonged period of observed stability. He was unfortunately admitted to intensive care 1 week later with septic shock, secondary to an *Escherichia coli* bacteraemia and cytomegalovirus

Fig. 1. Coronal reformatted images from Ga⁶⁸ DOTATATE whole-body fused PET-CT scan. **i** Intensely DOTATATE avid soft tissue within the SMV lumen demonstrates an SUV_{max} of 24. This was initially reported as nodal disease; however, review of diagnostic post-iodinated contrast CT (Fig. 2, 3) revealed the tumour recurrence to be intravascular. PET, positron emission tomography; CT, computed tomography; SMV, superior mesenteric vein.

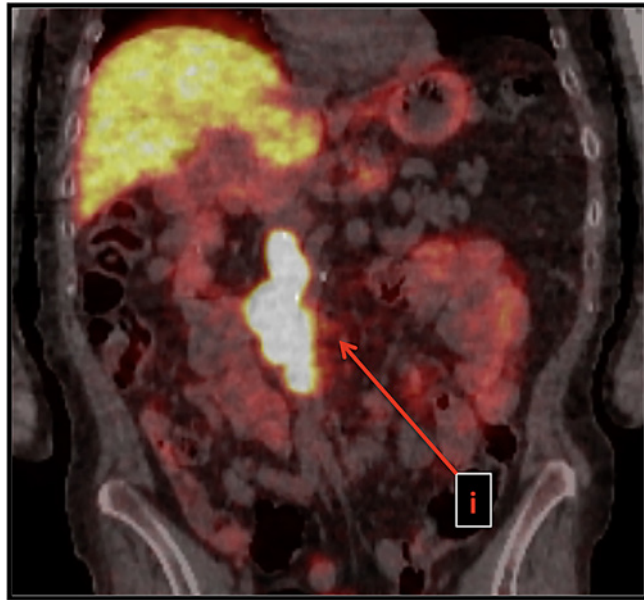
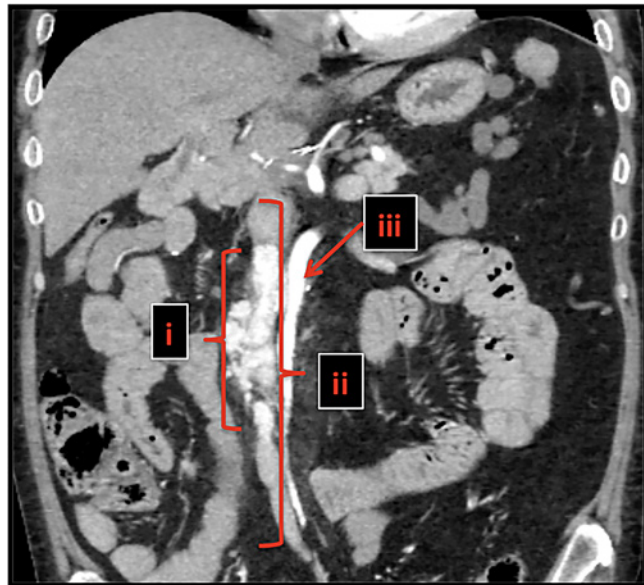


Fig. 2. Coronal reformatted images from arterial phase post-iodinated contrast CT scan. A large volume of tumour (**i**) has invaded the SMV (**ii**). The tumour demonstrates intense arterial hyper-enhancement compatible with NET; it is similar in density to the adjacent SMA (**iii**). **i** Hypervascular tumour invading lumen of SMV. **ii** SMV. **iii** Superior mesenteric artery. SMV, superior mesenteric vein.



viraemia. He was discharged to an inpatient rehabilitation facility after 5 weeks, bedbound due to significant deconditioning.

Soon after discharge, he developed worsening proximal myopathy, lower back pain, and unexplained ecchymosis and was re-admitted to our hospital. On physical examination, he was hypertensive at 162/107 mm Hg with ongoing unexplained oedema. Re-admission blood tests revealed a recurrence of hypokalaemia at 2.9 mmol/L with a hypernatraemia of 148 mmol/L and a metabolic alkalosis of pH 7.53 with a bicarbonate of 38.6 mmol/L. Review of recent imaging revealed osteoporotic vertebral compression fractures. He was investigated with a 24-h urinary free cortisol collection and low-dose dexamethasone test (Table 1), which confirmed a diagnosis of Cushing's syndrome. Baseline ACTH levels were elevated, and a high-dose dexamethasone suppression test was consistent with an ectopic ACTH source (Table 1).

Fig. 3. Coronal reformatted images from portal venous phase post-iodinated contrast CT scan. A large volume of tumour has invaded the SMV and occupies the lumen of the main SMV trunk (**ii**). This impairs splanchnic blood flow to the liver resulting in pre-hepatic mesenteric venous hypertension and the formation of mesenteric varices (**iv**). The small bowel varices are responsible for the clinical presentation of GI haemorrhage. **i** SMV. **ii** Tumour invading SMV. **iii** Superior mesenteric artery. **iv** Large varices in the small bowel and left upper quadrant. SMV, superior mesenteric vein.

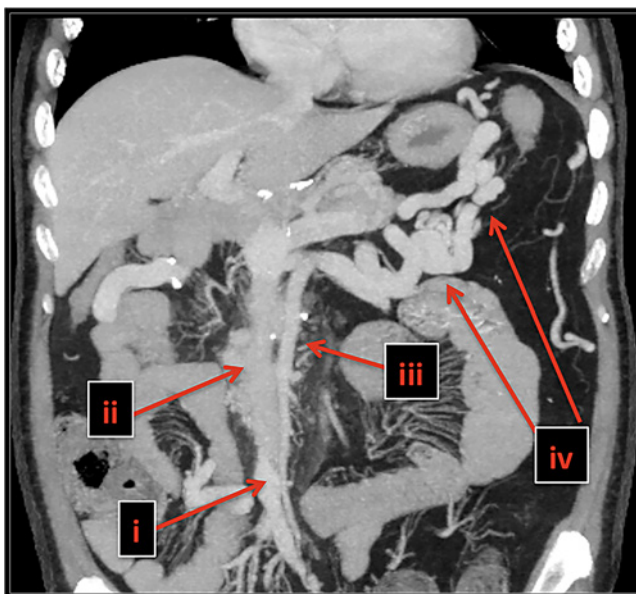


Table 1. Results confirming diagnosis of Cushing's syndrome secondary to ectopic ACTH release

| Test | Result (normal range) |
|--|-----------------------|
| Random 9 a.m. cortisol level, nmol/L | 581 (133–537) |
| 24-h urinary free cortisol, nmol/24 h | >2,170 (<200) |
| Morning cortisol level following late night 1 mg dexamethasone, nmol/L | 1,267 (133–537) |
| Morning cortisol level following late night 2 mg dexamethasone, nmol/L | 1,342 (133–537) |
| Morning cortisol level following late night 8 mg dexamethasone, nmol/L | 819 (133–537) |
| ACTH level following late night 8 mg dexamethasone, ng/L | 104 (0–46) |

ACTH, adrenocorticotrophic hormone.

Subsequent pituitary MRI and repeat gallium-68 DOTATATE PET scan revealed no other potential sources leading to a unifying diagnosis of Cushing's syndrome secondary to ectopic ACTH release from a recurrence of a pNET.

The patient was commenced on steroidogenesis inhibitors (metyrapone uptitrated to 1,000 mg 3 times per day and ketoconazole uptitrated to 200 mg 3 times a day) with oral hydrocortisone replacement of 10 mg twice a day, which gradually reversed his biochemical disturbance and normalized serum cortisol. He was discharged home after 27 days. Lanreotide therapy was continued, and serial imaging demonstrated a reduction in tumour size. The patient underwent community physiotherapy and has now regained a near pre-morbid performance status. As a result, at the time of writing, there are plans to start chemotherapy, with surgical resection felt to be too high risk due to the anatomical location of the tumour.

Discussion

The presentation of pNETs can vary greatly and can be a diagnostic challenge. This case demonstrates how the manifesting syndrome of a functional pNET can be insidious and the clinical evidence only fully appreciable with a retrospective eye. It also highlights the potential for serious sequelae from malignant invasion of surrounding structures.

Pancreatic malignancies are known to commonly abut or encase local vasculature and can cause obstruction either via external compression or bland thrombosis [10]. pNETs conversely are unique in their ability to cause tumour thrombosis and venous wall invasion, features not seen with pancreatic adenocarcinomas [10]. Historically, this was thought to be a rare occurrence [11]; however, a more recent study found evidence of local venous tumour thrombosis in 33% of CT scans of non-functional pNETs, with 62% of the initial scan reports omitting this finding [12]. A subsequent surgical study including both functional and non-functional pNETs found macroscopic venous invasion in 20% of cases [13] confirming this is a more common phenomenon than previously acknowledged.

It is essential that clinicians are aware of tumour thrombosis or direct venous wall invasion as potential complications of pNETs due to the risk of developing porto-mesenteric hypertension [10, 14]. This has been shown in a few case reports and a single retrospective study to lead to UGI haemorrhage; however, it is interesting to note that in all of these cases, gastric varices were identified as the source [15–17]. To the best of our knowledge, this is the first reported case of UGI bleeding from variceal mesenteric veins in the context of porto-mesenteric hypertension secondary to pNET vessel invasion. This is unsurprising given that ectopic varices, which include mesenteric and duodenal varices, are a rare cause of UGI bleeding, responsible for only 2–5% of all variceal bleeds of any aetiology [18]. They are nonetheless clinically relevant due to their increased propensity to bleed and associated high mortality rate [18, 19]. Fortunately, such catastrophic bleeding was not witnessed in this case, possibly explaining the negative video capsule endoscopy and successful conservative management.

ACTH-secreting pNETs are a rare occurrence with <0.1% of all pNETs each year diagnosed as ACTHomas [4]. Almost all are associated with advanced, metastatic disease [4, 9]; however, this case has demonstrated the potential for a clinically relevant ectopic Cushing's syndrome even with a localized tumour. Optimal management of ectopic Cushing's syndrome usually involves surgical resection of the pNET [7]. If this it is not feasible, as in this case, then treatment should aim to medically manage the tumour with anti-cancer therapies, whilst normalizing serum cortisol. The latter can be achieved via steroidogenesis inhibitors, such as metyrapone, ketoconazole, or mitotane, or with bilateral adrenalectomy in refractory cases [20].

pNETs are known to be pluripotent; however, this case has demonstrated an unusual situation wherein a non-functional pNET which was fully resected recurred many years later as a functional ACTH-secreting malignancy. This rare occurrence has only been reported in a limited number of other cases in the literature [21–23] and highlights the truly dynamic potential of pNETs. It is essential that clinicians are aware of possible changes in tumour functionality with disease recurrence as this may complicate diagnosis and management.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and all accompanying images. No ethical approval was required for this case report as per national UKRI Medical Research Council and NHS Health Research Authority guidelines.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of this case report.

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Author Contributions

S.W. and K.P. wrote the manuscript. S.G., E.G., B.C.W., and R.S. revised the manuscript. S.G. provided and annotated the figures. S.W., E.G., S.G., B.C.W., and R.S. were involved in the care of the patient. All authors have approved the final version.

Data Availability Statement

All data referenced in this case report are included in this article. Further enquiries can be directed to the corresponding author.

References

- 1 Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "Carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*. 2008;26(18):3063–72.
- 2 Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology*. 2008;135(5):1469–92.
- 3 Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing but NET: a review of neuroendocrine tumors and carcinomas. *Neoplasia*. 2017;19(12):991–1002.
- 4 Ito T, Igarashi H, Jensen RT. Pancreatic neuroendocrine tumors: clinical features, diagnosis and medical treatment: advances. *Best Pract Res Clin Gastroenterol*. 2012;26(6):737–53.
- 5 Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol*. 2008;19(10):1727–33.
- 6 Mohapatra S, Enjamuri D, Velpari S, Korman A, Broder A. A rare case of upper gastrointestinal bleed: gastric metastasis of pancreatic neuroendocrine tumor. *Am J Gastroenterol*. 2018;113:S1118–9.
- 7 Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. *Lancet*. 2015;386(9996):913–27.
- 8 Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BMK, Colao A. Complications of Cushing's syndrome: state of the art. *Lancet Diab Endocrinol*. 2016;4(7):611–29.
- 9 Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, et al. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. *Neuroendocrinology*. 2012;95(2):98–119.
- 10 De Robertis R, Paiella S, Cardobi N, Landoni L, Tinazzi Martini P, Ortolani S, et al. Tumor thrombosis: a peculiar finding associated with pancreatic neuroendocrine neoplasms. A pictorial essay. *Abdom Radiol*. 2017;43(3):613–9.
- 11 Bok EJ, Cho KJ, Williams DM, Brady TM, Weiss CA, Forrest ME. Venous involvement in islet cell tumors of the pancreas. *AJR Am J Roentgenol*. 1984;142(2):319–22.
- 12 Balachandran A, Tamm EP, Bhosale PR, Katz MH, Fleming JB, Yao JC, et al. Venous tumor thrombus in nonfunctional pancreatic neuroendocrine tumors. *AJR Am J Roentgenol*. 2012;199(3):602–8.
- 13 Addeo P, d'Alessandro A, Averous G, Imperiale A, Faitot F, Goichot B, et al. Macrovascular venous invasion of pancreatic neuroendocrine tumours: impact on surgical outcomes and survival. *HPB*. 2019;21(6):653–61.
- 14 Köklü S, Çoban Ş, Yüksel O, Arhan M. Left-sided portal hypertension. *Dig Dis Sci*. 2007;52(5):1141–9.
- 15 Zaborowski A, Walsh SM, Ravi N, Reynolds JV. Pancreatic aetiology for massive upper gastrointestinal haemorrhage in pregnancy. *Case Rep Surg*. 2016;2016:1–4.

- 16 Terrell W, Lee S, Mulatre M. Acute gastrointestinal hemorrhage, sequela of pancreatic neuroendocrine tumor. Abstract 039 International Symposium on Endovascular Therapy Vascular Disease Management; 2020.
- 17 Moyana TN, Macdonald DB, Martel G, Pyatibrat S, Lee G, Capitano M. Pancreatic neuroendocrine tumors complicated by sinistral portal hypertension: insights into pathogenesis. *J Pancreat Cancer*. 2017;3(1):71–7.
- 18 Bhat AP, Davis RM, Bryan WD. A rare case of bleeding duodenal varices from superior mesenteric vein obstruction-treated with transhepatic recanalization and stent placement. *Indian J Radiol Imaging*. 2019 Jul-Sep; 29(3):313.
- 19 Ahmad S, Holdorf J, Oliveira P. Mesenteric variceal bleeding presenting as massive gastrointestinal bleeding. *Chest*. 2015;148(4):211A.
- 20 Nieman LK. Recent updates on the diagnosis and management of Cushing's syndrome. *Endocrinol Metab*. 2018;33(2):139–46.
- 21 Miehle K, Tannapfel A, Lamesch P, Borte G, Schenker E, Kluge R, et al. Pancreatic neuroendocrine tumor with ectopic adrenocorticotropin production upon second recurrence. *J Clin Endocrinol Metab*. 2004;89(8): 3731–6.
- 22 Rajeev S, McDougall S, Terlizzo M, Palmer D, Daousi C, Cuthbertson D. Evolution in functionality of a metastatic pancreatic neuroendocrine tumour (pNET) causing Cushing's syndrome: treatment response with chemotherapy. *BMC Endocr Disord*. 2014;14:70.
- 23 Simó-Servat A, Peiró I, Villabona C. Corticotropin secreting pancreatic neuroendocrine tumour, a therapeutic management challenge. A presentation of 2 cases. *Endocrinol, Diabetes Nutr (Engl Ed)*. 2019;66(3):204–6.