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Comment to: Patti ME, McMahon G, Mun EC et al. (2005) Severe hypoglycaemia post-gastric bypass requiring partial pancreatectomy: evidence for inappropriate insulin secretion and pancreatic islet hyperplasia. Diabetologia 48:2236–2240

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Abbreviations GLP-1: glucagon-like peptide 1

To the Editor:

We read the recent report of three cases of hypoglycaemia following gastric bypass surgery with interest [1]. Consistent with a prior study [2], the authors report postprandial hypoglycaemia in a subgroup of patients who had undergone gastric bypass surgery for morbid obesity. The authors speculate that ‘excessive secretion of GLP-1 played a pivotal role in post-gastric bypass hypoglycaemia in our second and third patients, and perhaps in the first.’ However, respectfully we suggest that the report contains insufficient evidence to support this intriguing conclusion.

The arguments provided by the authors in support of this conclusion are as follows: (1) two out of the three patients exhibited increased (~300 pmol/l) postprandial glucagon-like peptide 1 (GLP-1) plasma levels; (2) pancreatic sections from all three patients showed islets adjacent to exocrine ducts as well as single hormone-positive cells inside the ductal epithelium; (3) in one patient the frequency of Ki-67-positive cells appeared higher in exocrine ducts; and, (4) the relative beta cell area in one of the patients was reported to be relatively high (3.3%) compared with that in obese controls.

However, there is no evidence for a stimulatory role of GLP-1 on beta cell proliferation in humans in vivo. While we agree that this has been shown in rodents using pharmacological concentrations of GLP-1 [3], the capacity for beta cell replication in adult humans is much less than that in rats. Also, it would be of interest to know how the GLP-1 concentrations in people with symptomatic hypoglycaemia after gastric bypass surgery compared with those patients who did not have this symptom. While often interpreted as a marker of new islet formation [4], the presence of islet cells within or adjacent to exocrine ducts must be interpreted with caution; it is a common finding in adult human pancreas [5, 6] (Fig. 1). Also, lineage tracing studies in mice suggest that beta cell replication rather than new islet formation from ductal cells is the primary source of beta cell formation during adult life, though this may well be different in humans [7]. Ki67 staining has previously been described in ductal cells from adult human pancreas [5, 6], and in other pancreatic cell types, such as exocrine acinar cells or vascular endothelial cells [6]. To date, there is no evidence that the presence of Ki67 staining in ductal cells indicates increased beta cell formation rather than turnover of ductal cells. Also, the reported pancreatic area of 3.3% is well within the typical range for obese (mean 2.66%, range 0.7–10.5%) and lean (mean 1.71%, range 0.32–4.42%) humans [6]. This is presumably the basis of the statement that there was diffuse islet hyperplasia in all three cases, but we are unable to find any evidence to support this in the provided data. Islet density and islet size compared with controls were not reported.

We respectfully suggest caution before concluding that the data provided indicate a new clinical syndrome of postprandial hypoglycaemia due to expansion of beta cell mass secondary to excessive GLP-1 secretion. There is no reason to expect a high beta cell mass to cause hypoglycaemia in response to physiological stimuli, especially if GLP-1 is thought to be involved, which only stimulates insulin secretion in a strictly glucose-dependent manner [8]. In fact, the glucose-sensing machinery of pancreatic beta cells rep-

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Fig. 1 Two pancreatic sections stained for insulin (brown) and haematoxylin (blue) from a non-diabetic patient without a history of hypoglycaemia (age: 36 years, BMI: 36 kg/m², fractional beta cell area per total pancreatic area: 2.7%), who underwent surgery for removal of a benign pancreatic cyst. These images illustrate that the presence of multiple islets adjacent to exocrine ducts is a common finding in normal adult pancreas. Images were taken at 20× objective magnification

resents a potent safeguard against excessive insulin secretion [9]. Moreover, islet or beta cell hyperplasia would more likely be associated with autonomous insulin secretion, leading to fasting rather than postprandial hypoglycaemia. The report by Patti et al. also contains no information on whether accelerated gastric emptying (of the residual stomach) was present in the patients with postprandial hypoglycaemia compared with asymptomatic patients following gastric bypass [1]. Accelerated gastric emptying might be expected in the classic late dumping syndrome [10]. Perhaps abnormal counter-regulation to hypoglycaemia should be excluded as an alternative explanation for the symptomatic hypoglycaemia. Finally, perhaps the greatest argument against the conclusion that these symptoms were due to increased beta cell mass is the fact that an 80% pancreatectomy in case one provided no relief, and a distal pancreatectomy in case two provided only temporary relief of symptoms [1].

We certainly appreciate the dangerous nature of hypoglycaemia and note that two of the patients were involved in road traffic accidents attributed to hypoglycaemia. Indeed, one lesson is that in cases with recurrent unresolved hypoglycaemia, driving a motor vehicle is ill advised. None the less, the long-term clinical success of the surgical intervention selected for these patients needs to be critically assessed before this putative novel syndrome and its therapy can be accepted and pancreatic resections advised for patients presenting with reactive hypoglycaemia after bariatric surgery.

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