World Journal of Surgery

World J Surg (2007) 31: 444–445

Reply

DOI: 10.1007/s00268-006-0765-2
Published Online: 5 January 2007

We have read with interest the well taken queries put forward by Mishra *et al*. in response to our publication on islet-cell hyperplasia in adults[1] and would like to answer as follows:

1. Mishra *et al*. correctly noticed that in contrast to Service and Thompson,[2,3] we have seen both, fasting hypoglycemia and typical postprandial hypoglycemia, in most of our published patients. Since in our institution an initial oral glucose load routinely always precedes the standard fasting test as an integral part of this classical suppression test, there was no need to develop a specific diagnostic strategy in patients suspected to suffer from any form of clinically relevant hypoglycemia, be it classical insulinoma or NIPHS. Indeed, we strongly advocate initial glucose loading to precede the supervised fasting test. Any such procedure with the first sample drawn typically after an overnight fast would miss the postprandial phase during the night and be already in the 12th hour in most cases. As to our experience, a characteristic feature of our NIPHS patients was the presence of both, postprandial and fasting hypoglycemia with clinical neuroglycopenia and very modest ''relative'' hyperinsulinemia meaning clearly measurable insulin levels at concentrations > 0 mU/l.
2. After our initial experience with NIPHS patients, first thought to suffer from insulinoma and the necessity of reoperation because of initial limited pancreatic resection we always performed 75–80% resections in the absence of a palpable insulinoma despite the presence of documented neuroglycopenia in order to cure these patients. Since not all patients had calcium infusion tests (SACI) we opted for extended left side resections. Patients where preoperatice SACI had shown exaggerated insulin response in the head draining arteries only received right-sided head resections. Thus, patient 6 was operated in a different institution where an intraoperative SACI was performed due to the absence of a tumor. This proved pathological insulin stimulation in the gastroduodenal artery and we have performed a Whipple's procedure rather than a left sided resection during the second surgery.
   False positive imaging results have been published by other authors[4] and present an intriguing dilemma during the search for pancreatic lesions. Thus, endosonography may detect nodular pancreatic lesions in the absence of pancreatic disease. Additional problems, i.e., lymph nodes or investigative artifacts have been correctly pointed out my Mishra *et al*.
3. The typical histological features of nesidioblastosis or islet hyperplasia have been recently published by Anlauf *et al*.[5] stating clearcut differences as compared to normal pancreatic tissue. Other authors, however, failed to see such differences and even found (Goudswaard[6]) nesidioblastosis-like features in pancreatic tissue in patients without hyperplasia or hypoglycemia. Since Anlauf *et al*. investigated 5 of our patients from Duesseldorf with two patients suffering from a well defined insulinoma, a letter to the editor of the journal pointing towards this problem was recently published.[7,8] Altogether, we are certain that islet hyperplasia including regional differences and /or visualization of multiple microadenomas add to the clinical features of NIPHS. The discrimination between diffuse nesidioblastosis, regional nesidioblastosis, and multifocal regional microadenomas in the absence of MEN-I disease may as yet not be well defined, even not in patients with proven insulinoma.
4. Selective arterial calcium infusion undoubtfully proves pathological insulin hypersecretion. Though often ''mild'', it is helpful to confirm abnormal OGTT- and fasting test results as the biochemical feature of a regional insulin secreting source or the failure to adequately shut off insulin secretion. Therefore the surgeon is guided during the unease of blind resection of visually perfect looking pancreatic tissue. It determines whether pancreas should be resected from the left or the right side. Altogether, with such a rather

radical approach to sincerely suffering patients we now have cured 10 of 13 patients while 3 patients suffer mild diabetes mellitus postoperatively. None of our patients presently continues to suffer from hypoglycemic symptoms. We strongly advocate the SACI test in any patient with reproducible true neuroglycopenia – postpandially and/or during fasting – when the insulin levels are low or close to lower limits of detection but definitely not zero (< 3 mU/l).

We thank Mishra *et al*. for their interest in the topic and the thoughtful and important questions pointed out.

REFERENCES

1. Starke A, Saddig C, Kirch B, *et al.* Islet hyperplasia in adults: challenge to preoperatively diagnose non-insulinoma pancreatogenic hypoglycemia syndrome. World J Surg 2006;30:670–679.
2. Service FJ, Natt N, Thompson GB, *et al.* Noninsulinoma pancreatogenous hypoglycemia: a novel syndrome of hyperinsulinemic hypoglycemia in adults independent of mutations in Kir6.2 and SUR1 genes. J Clin Endocrinol Metab 1999;84:1582–1589.
3. Service GJ, Thompson GB, Service FJ, *et al.* Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. N Engl J Med 2005;353:249–254.
4. Kann PH, Wirkus B, Keth A, *et al.* Pitfalls in endosonographic imaging of suspected insulinomas: pancreatic nodules of unknown dignity. Eur J Endocrinol 2003;148: 531–534.
5. Anlauf M, Wieben D, Perren A, *et al.* Persistent hyperinsulinemic hypoglycemia in 15 adults with diffuse nesidioblastosis. Am J Surg Pathol 2005;29:524–533.
6. Goudswaard WB, Houthoff HJ, Koudal J, *et al.* Nesidioblastosis and endocrine hyperplasia of the pancreas: a secondary phenomenon. Hum Pathol 1986;17:46–54.
7. Goretzki P, Starke A. Coincidence of insulinoma with nesidioblastosis or false diagnosis in 2 of 15 patients? Am J Surg Pathol 2006;30:919–920, (letter).
8. Anlauf M, Wieben D, Klöppel G, *et al.* Diffuse nesidioblastosis in adults and insulinoma: can they be associated ? Am J Surg Pathol 2006;30:919–920, (letter).

Achim Starke

Department of Endocrinology & Diabetology
University of Düsseldorf
Düsseldorf, Germany
e-mail: starkea@uni-duesseldorf.de