Who should be tested for gastroparesis among diabetic patients

To the Editor,

We read with great interest the paper "Diabetes is not an independent predictor of gastroparesis in symptomatic patients referred for gastric emptying studies" published in the March 2010 issue of your journal [1]. The authors' conclusion is that diabetes mellitus is not an independent predictor of gastroparesis in patients with gastrointestinal (GI) symptoms who are referred for gastric emptying studies.

After auditing a series of gastric emptying tests performed by scintigraphy, the authors pertinently report that those cases with prolonged gastric emptying cannot be a predictor of whether they have or do not have diabetes mellitus. They also confirm previous data that there is no relationship between upper GI symptoms and gastric emptying in diabetic patients [2, 3].

The main practical problem of this issue is: should we refer patients with diabetes mellitus to gastric emptying tests? And if yes, what ones?

Many patients with a long history of diabetes mellitus develop autonomous neuropathy with gastroparesis. The gastric transit time is not necessarily related to dyspeptic symptoms and the upper digestive symptoms are not related to autonomic neuropathy of other systems, i.e. the cardiovascular system [3]. There are many studies showing that the correlation between delayed gastric emptying and upper GI symptoms is weak although the prevalence of gastroparesis in long-standing diabetes mellitus ranges from 25-55% in type 1 diabetes [4] to 30% in type 2 diabetes mellitus [4]. Prokinetic agents are however able to improve symptoms [5]. Personality factors are also involved in the reporting of dyspeptic symptoms in diabetes [4], and these are independent of gastroparesis.

On the other hand, more than half of the diabetic patients with severe delay in gastric emptying may present no symptoms at all [6], therefore are not submitted to the assessment of gastric emptying; thus, the prevalence of gastroparesis in diabetes mellitus may be largely underestimated.

It seems that patients with asymptomatic gastroparesis have unstable diabetes, as shown in more than one study. Glycemic control might be disturbed particularly in those with type 1 diabetes, due to a mismatch between the food absorption and the action of exogenous insulin [6].

Referring patients to scintigraphic assessment of gastric emptying is biased through the concerns of physicians and patients regarding the potential harm of this radioisotopic method, although delayed radionucleotide gastric emptying studies can predict morbidity in diabetics with symptoms of gastroparesis [7]. An alternative would be the use of ^{13}C breath tests, which has a good correlation with the scintigraphy [7].

We feel that the study by Gumaste et al [1] is very important not only for being the first one (as the authors stated) to analyze whether diabetes is an independent determinant of gastroparesis in patients with GI symptoms, but also because it is a warning with regard to the inappropriate referral to radioisotopic gastric emptying testing.

We empirically recommend performing gastric emptying tests in patients with a history of diabetes mellitus for several years, if they have upper digestive symptoms not explained by upper digestive endoscopy; or if they have unstable diabetes while on appropriate insulin or oral therapy. Excluding research purposes, gastric emptying tests should not be performed in all patients with a long history of diabetes. A better selection of patients for gastric scintigraphy would increase the yield of the method.

A prospective protocol examining the assessment of gastric emptying by scintigraphy in consecutive patients with long-lasting diabetes mellitus (CNCSIS grant No. 1277/2008) will hopefully show us, based on evidence, if we should routinely measure gastric emptying in this condition.

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Reply

Despite a scientifically weak association between rates of gastric emptying and symptomatology in diabetic patients [1], physicians continue to reflexively order gastric scintigraphic studies in patients with diabetes mellitus who present with upper gastrointestinal problems. Our study [2], though limited by its retrospective design, clearly indicated a lack of evidence for this erroneous practice.

We thank Poanta and Dumitrascu for their positive remarks with regard to our study and for suggesting that it should serve as a ‘warning with regard to the inappropriate referral to radioisotopic gastric emptying testing.’ Moving forward, we enthusiastically endorse the attempts by the authors to formulate a prospective protocol to validate the findings of our study. Hopefully the authors will also evaluate the role of other factors like age and gender that do contribute to gastric emptying and come up with a comprehensive guideline for gastric scintigraphic referral [3, 4].

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Paravaterian diverticula presenting as acute cholangitis in two very elderly patients

To the Editor,

We present a rather unusual cause of acute cholangitis occurring in two very elderly patients. In the first case, a 92-year-old man was hospitalized because of constrictive epigastric pain inconstantly radiating to the left shoulder. His medical history was noticeable for chronic obstructive pulmonary disease (COPD), coronary heart disease, and Helicobacter Pylori- related gastritis eradicated 4 years before. The abdomen was tender in the epigastrium and the right upper quadrant, and bowel movements were present. The liver margin was smooth, slightly tender and palpable at 2 cm from the lower ribs. On day 2, the patient developed jaundice, fever and continuous epigastric pain. Blood tests showed a cholestatic pattern. Serum amylase and lipase levels were normal, thus excluding acute pancreatitis. A blood culture grew Klebsiella Pneumoniae. An ultrasound of the upper abdomen showed a liver of normal size, shape and structure; the biliary tree was mildly dilated, but the terminal part of the common bile duct was not visible. The gallbladder was dilated, with regular walls, and contained echogenous material compatible with biliary sludge. A diagnosis of acute cholangitis was made. Antibiotic therapy with ceftriaxone and intravenous fluids were started. A cholangio-NMR of the upper abdomen showed the presence of a paravaterian diverticulum located cranially to the papillary outlet in the duodenal lumen and excluded the presence of gallstones in the gallbladder and the biliary tree (Fig. 1). The patient experienced a steady improvement of the clinical picture and was discharged on day 10 after admission. No recurrence of the pancreatico-biliary symptoms was observed at 1 year of follow-up.

In case 2, a 92-year-old woman was admitted to our unit because of intermittent fever. Her medical history included an acute cholangitis occurring three months earlier, secondary to multiple stones in the common bile duct which were removed by endoscopic papillotomy. The patient was febrile, sweating, confused and not compliant. The abdomen was tender in the right hypochondrium, and bowel sounds were reduced. Blood tests revealed hepatic cytolysis and mild cholestasis. A liver ultrasound showed several gallstones in the common bile duct, but not in the gallbladder. The biliary tree was dilated. A diagnosis of recurrent choledocolithiasis complicated with acute cholangitis was made. Ceftriaxone was started but four days later fever and abdominal pain persisted, so an ERCP was performed. Four small stones were removed from the

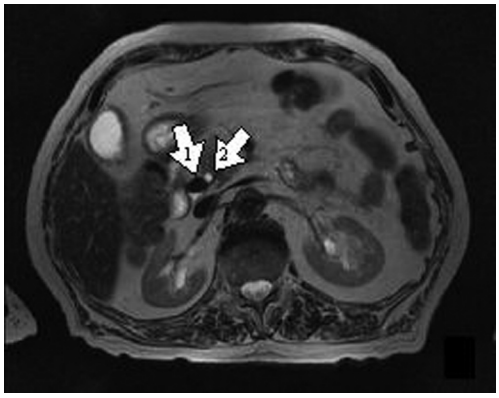

Fig 1. Abdominal cholangio-MR - T2 weighted images: arrow 1 highlights the duodenal diverticulum, in its lumen the contrast medium forms a little hydro-aerial level; arrow 2 indicates the mildly dilated common bile duct.

common bile duct, and the presence of a diverticulum located cranially to the papilla of Vater was noticed. A blood culture was positive for Staphylococcus Epidermidis, so antibiotic therapy was switched to levofloxacin and trimethoprim-sulfamethoxazole. The patient became afebrile and a steady normalization of liver function tests was observed. She was discharged after completing a 10 day antibiotic therapy and is well at 1 year of follow-up.

Periampullary diverticula (PAD), also called paravaterian diverticula, are extraluminar outpouchings of the duodenal lumen arising in a range of 2-3 cm from the ampulla of Vater. Their prevalence ranges from 0.16% to 27% and increases with age [1]. The association between PAD and cholangitis is debated: cholangitis can occur secondarily to the presence of stones in the biliary tract, but the possibility that paravaterian diverticula can cause cholangitis per se (i.e. in the absence of gallstones) is still controversial. Such an occurrence has been defined as Lemmel's syndrome. The hypothesized mechanisms are abnormality of the papillary motility, bacterial contamination and compression ab extrinseco of the main biliary duct. The therapeutic options for PAD include surgical diverticulectomy, ERCP with papillotomy and/or a medical approach. Open-surgery of diverticula is currently limited to emergency surgery in the case of perforation or bleeding. ERCP with sphincterotomy is the technique of choice for PAD treatment, and is efficacious and safe also in the very old (≥90 years) [2]. However, diverticula arising close to the ampulla can make the ERCP technically difficult, and a greater rate of complications due to the procedure has been reported [3]. Success rates, though, seem similar in patients with and without PAD [4]. To our knowledge, studies assessing the long-term benefits by the endoscopic technique are still limited by single centre series [5].

In **conclusion,** paravaterian diverticula may cause cholangitis per se, without direct evidence of bile duct stones. The choice of a therapeutic approach in patients with complicated paravaterian diverticula should be based on the evolution of the clinical picture, as there are no guidelines addressing the management of this disease, especially in the very elderly.

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Decreased beta cell reserve and higher prevalence of vascular complications in cirrhotics who developed diabetes mellitus

To the Editor,

Insulin resistance could be a primary event complicating liver cirrhosis (LC), but additional β-cell secretory defects are crucial for the development of diabetes mellitus (DM) [1].

We evaluated the insulin secretion and beta cell reserve with the homeostasis model assessment - HOMA β (%) = I x 360 / G -63 (≤ 80% indicating pathological value), the Child-Pugh score, the complications of LC and DM, as well as the 5 year survival in 49 patients with alcoholic and viral C cirrhosis who had developed DM.

A diminished β-cell reserve (<80%) was recorded in 24% of the DM patients. A β-cell reserve of >80% was found in 22% of the cirrhotics with DM and in 17% of those having an impaired glucose test (IGT). Thirteen out of 18 cirrhotics who deceased within 5 years had DM and IGT. Cardiovascular and hepatic complications were almost equally responsible for the death of patients (8 vs 7).

The fact that the β-cell reserve in one of four of our LC plus DM patients decreased may be partially explained by the frequently associated chronic pancreatic damage and injury of pancreatic islet beta cells in chronic alcoholism, resulting in lower insulinemia and DM [2-4] when acting on a chronic insulin resistance state. Perseghin et al [1] found that liver transplantation, by decreasing insulin resistance,

cured hepatogenous diabetes in 67% of cirrhotic-diabetic patients; nevertheless, 33% were still diabetics because of the persistence of a reduced β-cell function.

The increased prevalence of cardiovascular complications in our cirrhotics, in contrast with other reported groups [5, 6], could be due to the atherogenic lipid profile and hepatic steatosis accompanying chronic alcoholism and viral C infection as metabolic syndrome components, thus increasing the cardiovascular risk in liver cirrhosis. Therefore, alcoholic LC followed by development of DM has similar evolution and complications as the hepatogenous diabetes of non alcoholic LC patients accompanied by metabolic syndrome.

In **conclusion**, both insulin resistance and decreased β-cell reserve in liver cirrhosis followed by diabetes are important determinants of the degree of oral glucose tolerance. Mortality due to vascular complications is higher in patients with alcoholic liver cirrhosis associated with diabetes mellitus.

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Mesalazine induced drug fever

To the Editor,

We would like to report a patient who developed fever after mesalazine administration for ulcerative colitis, which disappeared when mesalazine was stopped.

A newly diagnosed patient with ulcerative colitis was referred to our hospital because of fever. He was a 23-year old man who had presented with bloody diarrhea to a state hospital, colonoscopy had showed pancolitis with superficial ulcerations and exudation. Mesalazine 4.5 g /day had been started. On the 4th day of treatment with mesalazine a fever of 40°C developed with chest pain and myalgia. After the diagnosis of pericardial effusion on echocardiography, 55 mg oral prednisolone per day was given. The fever and pericardial effusion had disappeared first but fever had reappeared when prednisolone was tapered to 5 mg per day. When he was referred to our clinic, he was using 5 mg prednisolone and 3 g mesalazine. Laboratory examination showed a high erythrocyte sedimentation rate (100 mm per hour), a high CRP level (133 mg/dL) and iron deficiency anemia. Chest X-ray and echocardiography were normal. Urine and blood cultures remained sterile. Urinary PCR investigation for tuberculosis and Quantiferon-TB test were negative. Autoimmune and viral markers were negative. A thorax CT scan evidenced small axillary lymph nodes and abdominal CT scan showed small inguinal lymph nodes. Inguinal lymph node biopsy showed reactive hyperplasia. Bone marrow biopsy was performed and was normal. On the 10th day of administration, mesalazine was stopped. Fever disappeared on the second day and did not reoccur. CRP and sedimentation rate returned to normal. After two weeks of abstinence we discussed the situation with the patient and decided to perform a challenge test with 250 mg of mesalazine. On the 3rd day of mesalazine he developed again a fever of 40°C, so we stopped this therapy permanently. At this time there was no sign or symptom of pericarditis.

Mesalazine induced fever without other associated symptoms was reported by Gonzalo et al, in this case the causal relation was proved by a placebo-controlled challenge test and a protocol of desensitization was realized successfully [1]. Pericarditis associated with inflammatory bowel disease can be related to hypersensitivity reaction to mesalazine therapy, but it has been also reported as an initial manifestation of inflammatory bowel disease or in patients on chronic therapy [2, 3]. In our case pericarditis and fever were resolved by corticosteroid therapy first, but fever reappeared when the dose was tapered. During hospitalisation there was no sign of pericarditis, and the colitis was clinically in remission. We excluded other causes of fever. As the fever was resolved when mesalazine was stopped and reoccurred only when it was started again, we concluded that the patient's fever was related to mesalazine.

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Parallel manifestation of Crohn's disease and acute pericarditis: a report of two cases. Int J Colorectal Dis 2007; 22: 1123-1125.

Gastric penetration by an ingested sewing needle with migration to the liver

To the Editor,

A 21-year-old man with mental retardation was admitted after his mother reported that he had swallowed a metallic foreign body (tweezer) accidentally three days ago, presenting abdominal pain and irritability, loss of appetite and diarrhea.

On admission, he was mildly pyrexial (37.6°C), with mild tenderness over the entire abdomen but without signs of peritoneal irritation. Laboratory tests showed mild anemia (hematocrit 34.2%; hemoglobin 11.5 g/dl). His white blood cell count was 12,250/mm^{3,} with 80% neutrophils. Serum concentration of C-reactive protein was elevated (2.1 mg/dl). Liver function tests were abnormal: aspartate aminotransferase, 345 U/L; alanine aminotransferase, 287 U/L; alkaline phosphatase, 244 U/L; gamma-glutamyl transpeptidase, 326 U/L; total bilirubin 2.7 mg/dl and direct bilirubin, 1.1 mg/dl.

An abdominal radiograph revealed the ingested object in the right abdomen (presumably in the ascending colon). A second radiopaque object looking like a sewing needle was also incidentally found in the upper abdomen (Fig. 1). No free abdominal air was observed. There was no history of needle swallowing or previous abdominal operation. Upper gastrointestinal endoscopy showed no overt perforation or foreign body in the esophagus, stomach or duodenum. On the next day, the ingested object was passed along with feces but the needle was still present in the same location on a repeat radiograph. Computed tomography without contrast showed a thin, hyperdense object located along the hepatoduodenal ligament in an anteroposterior axis, with a tilt from posterior lateral to midline anterior. The tip of the needle was located near segment I of the liver, in close relation to the inferior vena cava (Fig. 2).

On laparotomy, loose adhesions were found between the stomach and the left liver lobe. After adhesiolysis, the tip of the needle was found to be lodged 2 cm deeply into the first hepatic segment close to the inferior vena cava while the eye end was fixed by fibrotic tissue to the superior edge of the prepyloric antrum. The rusted 5-cm needle was dissected freely and extracted without complications. The postoperative course was uncomplicated, abnormal levels of biochemical variables returned back to normal three days after surgery.

Perforation of the gastrointestinal tract by an ingested sewing needle with subsequent migration into the liver is extremely rare. The perforation occurs usually at sites of physiological narrowing of the gastric [1-3] or duodenal wall [4-6]. This is a slow process allowing development of an inflammatory/fibrotic reaction which results in adhesion formation thus preventing free intraperitoneal perforation and peritonitis. Most patients are asymptomatic; an ingestion history is often missing and the diagnosis is made mostly incidentally [1, 3-5].

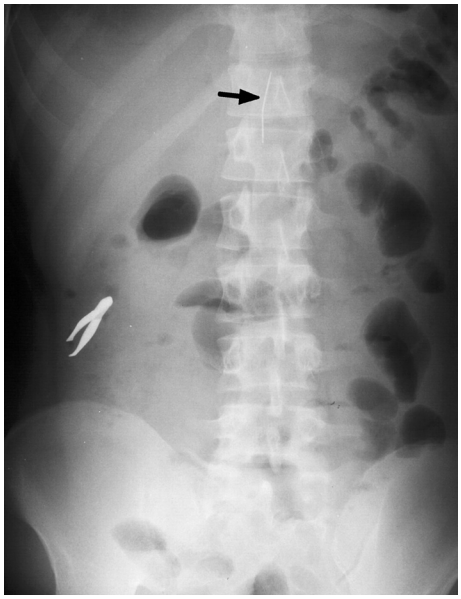

Fig 1. Plain abdominal radiograph showing the ingested tweezer and a needle-like object in the upper abdomen (arrow).

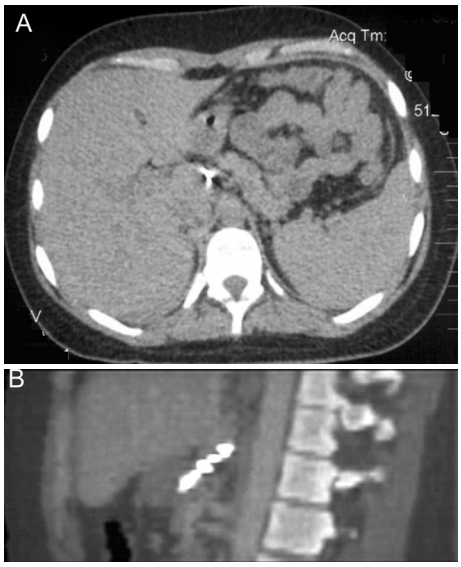

Fig 2. Plain abdominal CT images. Axial (A) and sagittal view of the reconstructed image (B) showing the needle as a linear radiopaque density located in segment I of the liver and close to inferior vena cava.

Endoscopy may reveal the ingested needle protruding from the gastric or duodenal wall and can be used for its removal. Computed tomography is the preferred technique for detection and accurate localization of the migrated needle especially when abscess formation is suspected.

Although conservative management has been described for asymptomatic patients with a stable, uncomplicated needle, prophylactic extraction should be undertaken

through laparotomy [1, 2, 6] or laparoscopy [4, 5] to avoid complications such as hemorrhage, abscess or fistula formation.

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