GASTROENTEROLOGY 2009;137:532–540

CLINICAL ADVANCES IN LIVER, PANCREAS, AND BILIARY TRACT

Prospective Study of the Long-Term Effects of Bariatric Surgery on Liver Injury in Patients Without Advanced Disease

PHILIPPE MATHURIN,[*,‡] ANTOINE HOLLEBECQUE,[*,‡] LAURENT ARNALSTEEN,[§,‖] DAVID BUOB,[¶] EMMANUELLE LETEURTRE,[¶] ROBERT CAIAZZO,[§,‖] MARIE PIGEYRE,[#] HÉLÈNE VERKINDT,[‖] SÉBASTIEN DHARANCY,[*,‡] ALEXANDRE LOUVET,[*,‡] MONIQUE ROMON,[#] and FRANÇOIS PATTOU[§,‖]

Service d'Hépato-Gastroentérologie, ‡Unité Inserm U 795, §Unité Inserm U 859, Services de, ‖Chirurgie Endocrinienne, ¶d'Anatomie Pathologique, #de Nutrition, CHRU de Lille, Université Lille 2, France

BACKGROUND & AIMS: Severe obesity is implicated in development of nonalcoholic fatty liver disease (NAFLD). Bariatric surgery induces weight loss and increases survival time of obese patients, but little is known about its effects on liver damage. We performed a 5-year prospective study to evaluate fibrosis and nonalcoholic steatosis (NASH) in severely obese patients after bariatric surgery. **METHODS:** Bariatric surgery was performed on 381 patients. Clinical and biological data, along with liver biopsies, were collected before and at 1 and 5 years after surgery. **RESULTS:** Five years after surgery, levels of fibrosis increased significantly, but 95.7% of patients maintained a fibrosis score ≤ F1. The percentage of patients with steatosis decreased from 37.4% before surgery to 16%, the NAFLD score from 1.97 to 1, ballooning from 0.2 to 0.1. Inflammation remained unchanged. The percentage of patients with probable or definite NASH decreased significantly over 5 years, from 27.4% to 14.2%. The kinetics of insulin resistance (IR) paralleled that of steatosis and ballooning; the greatest improvements occurred within the first year and were sustained 5 years later. Steatosis and ballooning occurred more frequently in patients with a refractory IR profile. In multivariate analysis, the refractory IR profile independently predicted the persistence of steatosis and ballooning 5 years later. **CONCLUSIONS: Five years after bariatric surgery for severe obesity, almost all patients had low levels of NAFLD, whereas fibrosis slightly increased. Steatosis and ballooning were closely linked to IR; long-term effects could be predicted by early improvement in IR.**

Severe obesity is associated with decreased life expectancy of an estimated 5–20 years.[1–4] In terms of organ injury, severe obesity is implicated in development of nonalcoholic fatty liver disease (NAFLD).[5–10] The conceptual model of NAFLD has been referred to as the "2-hit hypothesis," with accumulation of fat as the first hit and development of an inflammatory response in fatty liver as the second.[5,7,11–23] In the first hit, accumulation of fat in hepatocytes renders the liver more vulnerable to subsequent insults.

In obese patients, bariatric surgery induces weight loss,[24–28] ameliorates cardiovascular risk factors,[29–32] and improves long-term survival, as shown by 2 recent studies.[33,34] At present, it has become mandatory to determine whether side effects will develop over the long term. Among potential side effects, evaluation of liver injury is essential because of liver failure in obese patients treated with jejunoileal bypass, a historical procedure that is no longer used.[35,36] Although liver injury in patients treated with the most recent bariatric surgical procedures (biliointestinal bypass, gastric bypass, gastric band) improves over the short term,[37–39] suspicions persist about fibrosis progression, because no data involving long-term follow-up with consecutive liver biopsies are available. Only long-term prospective studies will determine whether bariatric surgery exacerbates fibrosis progression.

Analysis of mechanisms implicated in the long-term effects of bariatric surgery requires an objective scale of obesity-induced organ injury. For this purpose, liver is an interesting organ because clinicians have at their disposal histologic quantification of degree of steatosis, a useful, reproducible, and robust method with intraobserver variability of 0.98.[40] This more in-depth comprehension of long-term evolution in the liver may be extended to other organs for which robust methods of quantification of early injury are not yet available.

Abbreviations used in this paper: ALT, alanine aminotransferase; BMI, body mass index; GGT, γ-glutamyl transferase; IR, insulin resistance; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD score; NASH, nonalcoholic steatosis.

0016-5085/09/$36.00
doi:10.1053/j.gastro.2009.04.052

Evolution of insulin resistance (IR) is a relevant parameter because of its correlation with cardiovascular risk factors[29–31] and its involvement in obesity-induced liver injury. In a prospective study, we observed that patients with a refractory insulin profile 1 year after surgery were more resistant to the beneficial effects of surgery on liver injury.[39] Nevertheless, the usefulness of this criterion in prediction of long-term evolution of liver injury warrants attention.

In this first prospective study focusing on long-term evolution of obesity-induced liver injury, we concurrently evaluated both the evolution of liver injury with the use of sequential biopsies and IR before and 1 and 5 years afterward in a large cohort of unselected severely obese patients treated by bariatric surgery. The aims were (1) to evaluate long-term evolution of fibrosis and histologic features of NAFLD and (2) to more comprehensively elucidate the long-term evolution of obesity-induced liver injury.

Patients and Methods

Patients

Between 1994 and December 2005, 444 severely obese patients were referred to our unit for evaluation in view of bariatric surgery. The latter was performed in 381 patients, but not in 63 others, for the following reasons: anatomical, as specified by the surgeon (n = 7); anesthetic, mainly related to respiratory or cardiac diseases (n = 5); patient renouncement (n = 24);, psychiatric disorders (n = 6); renal failure (n = 1); diagnosis of cirrhosis assumed from biological or clinical features (n = 14); unspecified hepatic reasons (n = 2); and unknown reasons (n = 4). To be eligible for the study, all patients had to have fulfilled the following criteria: (1) morbid obesity (body mass index [BMI; in kg/m^2] > 40) or severe obesity (BMI > 35), at least one comorbidity factor (arterial hypertension, diabetes mellitus) for ≥ 5 years, and resistance to medical treatment; (2) absence of medical or psychological contraindications for bariatric surgery; (3) absence of current excessive drinking, as defined by average daily consumption of alcohol of 20 g/d for women and 30 g/d for men, and no history of past excessive drinking for a period > 2 years at any time in the past 20 years; (4) absence of long-term consumption of hepatotoxic drugs; and (5) negative screening for chronic liver diseases, including negative testing for hepatitis B surface antigen and hepatitis C virus antibodies, and no evidence of genetic hemochromatosis.

Methods

The surgeon examined all patients and explained in detail the procedures of biliointestinal bypass, gastric bypass, and gastric band surgery (standardized information). From 1994 to 2001, only biliointestinal bypass and the gastric band were proposed. After 2001, gastric bypass was performed. Starting in 2004, biliointestinal bypass was no longer performed and was completely replaced by gastric bypass. Body weight and height were measured. When surgery was planned, patients were free to choose the surgical procedure. Informed written consent was obtained from all patients, and the study was conducted in conformity with the Helsinki Declaration. The biliointestinal bypass described by Eriksson[41] consisted of jejunoileostomy coupled with cholecystojejunal anastomosis. The second bariatric procedure consisted of an adjustable gastric band inserted by laparoscopy (Lap–Band System; INAMED Health, Santa Barbara, CA). The final procedure was a Roux en-Y gastric bypass consisting of partitioning of the upper stomach to create a small gastric pouch and gastrojejunostomy to reestablish gastrointestinal continuity.[42]

The following clinical and biological features were assessed prospectively before and 1 and 5 years after surgery: weight, BMI, blood pressure, alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), prothrombin time, platelets, serum triglyceride, cholesterolemia, fasting blood glucose, and fasting insulin. Diabetes, hypercholesterolemia, and hypertriglyceridemia were defined as follows: fasting blood glucose > 1.26 g/L, cholesterolemia > 2.4 g/L, and serum triglyceride > 1.5 g/L.

IR was assessed with the quantitative insulin sensitivity check index (QUICKI). This method is significantly correlated with the hyperinsulinemic euglycemic glucose clamp and is considered a valid method for evaluating IR in obese patients.[43] The QUICKI was calculated with the following equation: QUICKI = 1/(log fasting insulin) + (log fasting plasma glucose). The IR index is equal to 1/QUICKI. We used the previously published criterion referred to as the "refractory IR profile," defined by an insulin resistance index at 1 year which was >3.13.[39]

Histologic Study

Liver biopsies were performed during the operative procedure on an average of approximately 1 and 5 years after surgery. Biopsies were routinely stained with hematoxylin-eosin and Masson's trichrome. Steatosis was quantified by the percentage of hepatocytes containing fat droplets (steatosis amount) and considered as present when the extent was >10%. With the NAFLD score (NAS), liver biopsies were classified by 2 pathologists (E.L. and D.B.) blinded to the order of the biopsies and clinical and biological data. Biopsies were assigned at random to the pathologists. The NAS is defined as the unweighted sum of scores for steatosis (0–3), lobular inflammation (0–3), and ballooning (0–2), thus ranging from 0 to 8. Nonalcoholic steatosis (NASH) was considered as "probable or definite" if the NAS was ≥3 and definite if the NAS was ≥5.[44] Liver fibrosis was assessed semiquantitatively with a 5-grade scale: F0 was normal; F1, focal pericellular fibrosis in zone 3; F2, perivenular and pericellular fibrosis confined to zones 2 and 3 with or