

L. Genser · C. Barrat

Bariatric-Metabolic Surgery versus Conventional Medical Treatment in Obese Patients with Type 2 Diabetes: 5 Year Follow-up of an Open-Label, Single-Centre, Randomised Controlled Trial

Mingrone G, Panunzi S, De Gaetano A, et al (2015) Lancet September [1]

Background: Randomised controlled trials have shown that bariatric surgery is more effective than conventional treatment for the short-term control of type-2 diabetes. However, published studies are characterised by a relatively short follow-up. We aimed to assess 5 year outcomes from our randomised trial designed to compare surgery with conventional medical treatment for the treatment of type 2 diabetes in obese patients.

Methods: We did our open-label, randomised controlled trial at one diabetes centre in Italy. Patients aged 30–60 years with a body-mass index of 35 kg/m² or more and a history of type 2 diabetes lasting at least 5 years were randomly assigned (1:1:1), via a computer-generated randomisation procedure, to receive either medical treatment or surgery by Roux-en-Y gastric bypass or biliopancreatic diversion. Participants were aware of treatment allocation before the operation and study investigators were aware from the point of randomisation. The primary endpoint was

the rate of diabetes remission at 2 years, defined as a glycated haemoglobin A1c (HbA1c) concentration of 65% or less (≤ 47.5 mmol/mol) and a fasting glucose concentration of 56 mmol/l or less without active pharmacological treatment for 1 year. Here we analyse glycaemic and metabolic control, cardiovascular risk, medication use, quality of life, and long-term complications 5 years after randomisation. Analysis was by intention to treat for the primary endpoint and by per protocol for the 5 year follow-up. This study is registered with ClinicalTrials.gov, number NCT00888836.

Findings: Between April 27, 2009, and October 31, 2009, we randomly assigned 60 patients to receive either medical treatment ($N = 20$) or surgery by gastric bypass ($N = 20$) or biliopancreatic diversion ($N = 20$); 53 (88%) patients completed 5 years' follow-up. Overall, 19 (50%) of the 38 surgical patients (seven [37%] of 19 in the gastric bypass group and 12 [63%] of 19 in the biliopancreatic diversion group) maintained diabetes remission at 5 years, compared with none of the 15 medically treated patients ($P = 0.0007$). We recorded relapse of hyperglycaemia in eight (53%) of the 15 patients who achieved 2 year remission in the gastric bypass group and seven (37%) of the 19 patients who achieved 2 year remission in the biliopancreatic diversion group. Eight (42%) patients who underwent gastric bypass and 13 (68%) patients who underwent biliopancreatic diversion had an HbA1c concentration of 65% or less (≤ 47.5 mmol/mol) with or without medication, compared with four (27%) medically treated patients ($P = 0.0457$). Surgical patients lost more weight than medically treated patients, but weight changes did not predict diabetes remission or relapse after surgery. Both surgical procedures were associated with significantly lower plasma lipids, cardiovascular risk, and medication use. Five major complications of diabetes (including one fatal myocardial infarction) arose in four (27%) patients in the medical group compared with only one complication in the gastric bypass group and no complications in the biliopancreatic diversion group. No late complications or deaths occurred in the surgery groups. Nutritional side-effects were noted mainly after biliopancreatic diversion.

Interpretation: Surgery is more effective than medical treatment for the long-term control of obese patients with type 2 diabetes and should be considered in the treatment

L. Genser (✉)

Service de chirurgie hépatobiliopancréatique,
transplantation hépatique, groupe hospitalier Pitié-Salpêtrière,
Assistance publique-Hôpitaux de Paris (AP-HP),
Paris, F-7513, France
Institut de cardiométabolisme et nutrition
(Institute of Cardiometabolism and Nutrition [ICAN]),
Pitié-Salpêtrière Hospital, F-7513 Paris, France
e-mail : Laurent.genser@gmail.com

C. Barrat (✉)

Service de chirurgie digestive et métabolique,
centre intégré nord francilien de l'obésité, hôpital Avicenne,
Assistance publique-Hôpitaux de Paris (AP-HP), UFR SMBH
« Léonard de Vinci », université Paris-XIII, 125, rue de Stalingrad,
F-93000 Bobigny, France
e-mail : Christophe.barrat@aphp.fr

algorithm of this disease. However, continued monitoring of glycaemic control is warranted because of potential relapse of hyperglycaemia.

Commentaires : Les résultats à deux ans de cette étude contrôlée randomisée (traitement médical intensif versus chirurgie : Roux-Y-gastric bypass : RYGB ou dérivation biliopancréatique : DBP), publiés dans le New England Journal of Medicine en 2012 [2] avaient clairement démontré la supériorité de la chirurgie (et particulièrement de la DBP) aussi bien sur le contrôle glycémique que sur la rémission du diabète de type 2. En effet, les 95 % des patients opérés d'une DBP étaient en rémission complète [3] et 75 % dans le groupe RYGB ($p = 0,001$). Nous attendions les résultats à cinq ans de cette étude avec impatience. L'efficacité de la chirurgie reste toujours supérieure à celle du traitement médical (54 % de rémission dans les groupes « chirurgie » versus 0 % dans le groupe traitement médical). Une récurrence du diabète était notée chez 44 % des patients après RYGB contre 28 % après DBP. Quatre-vingt-cinq pour cent des patients initialement diabétiques n'avaient aucun traitement antidiabétique à cinq ans (75 % après RYGB et 95 % après DBP). Au-delà, les auteurs montrent qu'à long terme ces interventions permettent de diminuer de manière significative le risque cardiovasculaire, d'améliorer la qualité de vie et préviennent la survenue des complications micro- et macrovasculaires du diabète chez les opérés, au prix d'une mortalité nulle et d'une morbidité chirurgicale maîtrisée. Cette étude randomisée démontre une fois de plus [4,5] que la chirurgie métabolique a une place dans l'algorithme thérapeutique du diabète de type 2 ; cependant, d'autres études randomisées sont nécessaires pour valider les résultats de ce travail et déterminer quelle procédure offre les meilleurs résultats ainsi que les meilleurs candidats dans cette indication.

Health-Care Costs over 15 Years after Bariatric Surgery for Patients with Different Baseline Glucose Status: Results from the Swedish Obese Subjects Study

Keating C, Neovius M, Sjöholm K, et al (2015) *Lancet Diabetes Endocrinol* November [6]

Background: Bariatric surgery prevents and induces remission of type 2 diabetes in many patients. The effect of preoperative glucose status on long-term health-care costs is unknown. We aimed to assess health-care costs over 15 years for patients with obesity treated conventionally or with bariatric surgery and who had either euglycaemia, prediabetes, or type 2 diabetes before intervention.

Methods: The Swedish Obese Subjects (SOS) study is a prospective study of adults who had bariatric surgery and

contemporaneously matched controls who were treated conventionally (age 37–60 years; BMI of ≥ 34 in men and ≥ 38 in women) recruited from 25 Swedish surgical departments and 480 primary health-care centres. Exclusion criteria were identical for both study groups, and were previous gastric or bariatric surgery, recent malignancy or myocardial infarction, selected psychiatric disorders, and other contraindicating disorders to bariatric surgery. Conventional treatment ranged from no treatment to lifestyle intervention and behaviour modification. In this study, we retrieved prescription drug costs for the patients in the SOS study via questionnaires and the nationwide Swedish Prescribed Drug Register. We retrieved data for inpatient and outpatient visits from the Swedish National Patient Register. We followed up the sample linked to register data for up to 15 years. We adjusted mean differences for baseline characteristics. Analyses were by intention to treat. The SOS study is registered with ClinicalTrials.gov, number NCT01479452.

Findings: Between Sept 1, 1987, and Jan 31, 2001, 2010 adults who had bariatric surgery and 2037 who were treated conventionally were enrolled into the SOS study. In this study, we followed up 4,030 patients (2,836 who were euglycaemic; 591 who had prediabetes; 603 who had diabetes). Drug costs did not differ between the surgery and conventional treatment groups in the euglycaemic subgroup (surgery US\$10,511 vs conventional treatment \$10,680; adjusted mean difference $-\$225$ [95% CI $-2,080$ to $1,631$]; $P = 0.812$), but were lower in the surgery group in the prediabetes ($\$10,194$ vs $\$13,186$; $-\$3,329$ [$-5,722$ to -937]; $P = 0.007$) and diabetes ($\$14,346$ vs $\$19,511$; $-\$5,487$ [$-7,925$ to $-3,049$]; $P < 0.0001$) subgroups than in the conventional treatment group. Compared with the conventional treatment group, we noted greater inpatient costs in the surgery group for the euglycaemic ($\$51,225$ vs $\$25,313$; $\$22,931$ [$19,001-26,861$]; $P < 0.0001$), prediabetes ($\$58,699$ vs $\$32,861$; $\$27,152$ [$18,736-35,568$]; $P < 0.0001$), and diabetes ($\$61,569$ vs $\$47,569$; $18,697$ [$9,992-27,402$]; $P < 0.0001$) subgroups. We noted no differences in outpatient costs. Total health-care costs were higher in the surgery group in the euglycaemic ($\$71,059$ vs $\$45,542$; $\$22,390$ [$17,358-27,423$]; $P < 0.0001$) and prediabetes ($\$78,151$ vs $\$54,864$; $\$26,292$ [$16,738-35,845$]; $P < 0.0001$) subgroups than in the conventional treatment group, whereas we detected no difference between treatment groups in patients with diabetes ($\$88,572$ vs $\$79,967$; $\$9,081$ [$-1,419$ to $19,581$]; $P = 0.090$).

Interpretation: Total health-care costs were higher for patients with euglycaemia or prediabetes in the surgery group than in the conventional treatment group, but we detected no difference between the surgery and conventional treatment groups for patients with diabetes. Long-term health-care cost results support prioritisation of patients with obesity and type 2 diabetes for bariatric surgery.

Commentaires : Cette étude épidémiologique est la suite des travaux fondateurs de la SOS study [7]. Les auteurs ont comparé les coûts de prise en charge globale (traitement, hospitalisation et soins externes) des patients obèses opérés par rapport aux patients traités médicalement suivant leur statut glycémique (euglycémique — intolérant au glucose et diabétique). À 15 ans, en dépit des nombreux bénéfices rapportés [7], la chirurgie bariatrique ne permet pas de diminuer les coûts de santé chez les opérés et est même associée à un surcoût significatif chez les non-diabétiques : patients euglycémiques (+\$22 390 [17 358–27 423]; $p < 0,0001$) ; intolérants au glucose (+\$26 292 [16 738–35 845]; $p < 0,0001$). Les coûts globaux sont comparables chez les patients diabétiques (+\$9 081 [–1419 to 19 581]; $p = 0,090$). Le seul bénéfice économique de la chirurgie est observé sur les coûts liés aux traitements et seulement chez les patients diabétiques. De fait, les auteurs suggèrent que la chirurgie bariatrique, pour des raisons économiques, doit être réservée en priorité aux patients diabétiques. Cette vision est à mettre en balance avec les bénéfices à long terme de la chirurgie (–30 % de mortalité à 16 ans, prévention du diabète chez les non-diabétiques opérés...) rapportés par la même équipe. La santé n'a pas de prix, mais elle a un coût...

The Gut Microbiome, Diet, and Links to Cardiometabolic and Chronic Disorders

Aron-Wisnewsky J, Clément K (2015) Nat Rev Nephrol December [8]

Cardiometabolic diseases (CMDs) have been associated with changes in the composition of the gut microbiota, with links between the host environment and microbiota identified in preclinical models. High-throughput sequencing technology has facilitated in-depth studies of the gut microbiota, bacterial-derived metabolites, and their association with CMDs. Such strategies have shown that patients with CMDs frequently exhibit enrichment or depletion of certain bacterial groups in their resident microbiota compared to healthy individuals. Furthermore, the ability to transfer resident gut microbiota from mice or humans into germ-free mouse models, or between human patients, has enabled researchers to characterize the causative role of the gut microbiota in CMDs. These approaches have helped identify that dietary intake of choline, which is metabolized by the gut microbiota, is associated with cardiovascular outcomes in mice and humans. Trimethylamine N-oxide (TMAO) — a metabolite derived from the gut microbiota — is also associated with poor cardiovascular outcomes in patients with cardiovascular disease and is

elevated in patients with chronic kidney disease (CKD). TMAO might represent a biomarker that links the environment and microbiota with CKD. This Review summarizes data suggesting a link between the gut microbiota and derived metabolites with food intake patterns, metabolic alterations, and chronic CMDs.

Commentaires : Cette revue de la littérature nous présente de manière précise et exhaustive les liens entre microbiote, régime et pathologies d'organe dans les maladies cardiométaboliques aussi bien chez les rongeurs que chez l'humain. Ce travail, à la différence d'autres articles précédemment publiés, ne commet pas l'erreur d'extrapoler à l'homme des données obtenues uniquement chez l'animal. Une mise à niveau incontournable qui démontre une fois de plus le rôle central du tractus digestif dans la pathogenèse de l'obésité et des maladies cardiométaboliques.

Surgical Models of Roux-en-Y Gastric Bypass Surgery and Sleeve Gastrectomy in Rats and Mice

Bruinsma BG, Uygun K, Yarmush ML, et al (2015) Nature Protocols March [9]

Bariatric surgery is the only definitive solution currently available for the present obesity pandemic. These operations typically involve reconfiguration of gastrointestinal tract anatomy and impose profound metabolic and physiological benefits, such as substantially reducing body weight and ameliorating type II diabetes. Therefore, animal models of these surgeries offer unique and exciting opportunities to delineate the underlying mechanisms that contribute to the resolution of obesity and diabetes. Here we describe a standardized procedure for mouse and rat models of Roux-en-Y gastric bypass (80–90 min operative time) and sleeve gastrectomy (30–45 min operative time), which, to a high degree, resembles operations in humans. We also provide detailed protocols for both pre- and postoperative techniques that ensure a high success rate in the operations. These protocols provide the opportunity to mechanistically investigate the systemic effects of the surgical interventions, such as regulation of body weight, glucose homeostasis and gut microbiome.

Commentaires : Ce travail publié par une équipe référente fait la synthèse des différents modèles de chirurgie bariatrique chez le rat et la souris. Les techniques et matériels nécessaires sont présentés. Ces modèles sont associés à une mortalité périopératoire non négligeable (environ 30 %), mais sont indispensables pour la compréhension des mécanismes impliqués, dans l'amélioration entre autres du statut glycémique/métabolique après chirurgie bariatrique [10].

Is Laparoscopic Sleeve Gastrectomy a Lower Risk Bariatric Procedure Compared with Laparoscopic Roux-en-Y Gastric Bypass? A Meta-Analysis

Zellmer JD, Mathiason MA, Kallies KJ, et al (2014) Am J Surg December [11]

Background: Laparoscopic Roux-en-Y gastric bypass (LRYGB) is the current “gold standard” bariatric procedure in the United States. Laparoscopic sleeve gastrectomy (LSG) has recently become a commonly performed procedure for many reasons, including patients’ perception that LSG has less complexity and invasiveness, and lower risk. Our objective was to review the literature and compare the leak rates, morbidity, and mortality for LRYGB versus LSG.

Methods: Publications from 2002 to 2012 with n greater than or equal to 25 and postoperative leak rate reported were included. Statistical analysis included chi-square according to patient number.

Results: Twenty-eight (10,906 patients) LRYGB and 33 (4,816 patients) LSG articles were evaluated. Leak rates after LRYGB versus LSG were 1.9% ($N = 206$) versus 2.3% ($N = 110$), respectively ($P = 0.077$). Mortality rates were 0.4% (27/7,117) for LRYGB and 0.2% (7/3,594) for LSG ($P = 0.110$). Timing from surgery to leak ranged from 1 to 12 days for LRYGB versus 1 to 35 days for LSG.

Conclusions: Leak and mortality rates after LRYGB and LSG were comparable. The appropriate procedure should be tailored based on patient factors, comorbidities, patient and surgeon comfort level, surgeon experience, and institutional outcomes.

Commentaires : Cette méta-analyse, comme celle de Chang et al. [12], s’est intéressée aux références « récentes » (morbidité périopératoire maîtrisée, mortalité quasi nulle) et traitant de la morbidité de ces deux techniques. Ce travail montre que le RYGB et la sleeve ont une morbidité précoce et tardive comparable (fistule : 1,9 vs 2,2 % NS ; hémorragies : 3 vs 2 %, $p = 0,001$; événements thromboemboliques : 0,7 vs 0,6 % NS ; réopérations : 4,4 vs 3,4 % NS) et une mortalité toutes deux non nulles mais comparables : 0,3 vs 0,2 % NS. De manière complémentaire, un travail récent mené sur les données PMSI en France a permis de montrer que la mortalité liée à la chirurgie avait considérablement diminué entre 2007 et 2012 (0,25 vs 0,08 % pour la sleeve et 0,36 vs 0,11 % après RYGB) [13].

Long-Term Metabolic Effects of Laparoscopic Sleeve Gastrectomy

Golomb I, Ben David M, Glass A, et al (2015) JAMA Surg [14]

Importance: The prevalence of laparoscopic sleeve gastrectomy (LSG) is increasing, but data on its long-term

effect on obesity-related comorbidities are scarce. Because the population of bariatric patients is young, long-term results of those comorbidities are highly relevant.

Objective: To investigate the long-term effects of LSG on weight loss, diabetes mellitus, hypertension, dyslipidemia, and hyperuricemia.

Design, setting, and participants: Cohort study using a retrospective analysis of a prospective cohort at a university hospital. Data were collected from all patients undergoing LSGs performed by the same team between April 1, 2006, and February 28, 2013, including demographic details, weight follow-up, blood test results, and information on medications and comorbidities.

Main outcomes and measures: Excess weight loss, obesity-related comorbidities, and partial and complete remission at 1, 3, and 5 years of follow-up.

Results: A total of 443 LSGs were performed. Complete data were available for 241 of the 443 patients (54.4%) at the 1-year follow-up, for 128 of 259 patients (49.4%) at the 3-year follow-up, and for 39 of 56 patients (69.6%) at the 5-year follow-up. The percentage of excess weight loss was 76.8%, 69.7%, and 56.1%, respectively. Complete remission of diabetes was maintained in 50.7%, 38.2%, and 20.0%, respectively, and remission of hypertension was maintained in 46.3%, 48.0%, and 45.5%, respectively. Changes in high-density lipoprotein cholesterol level (mean [SD] level preoperatively and at 1, 3, and 5 years, 46.7 [15.8], 52.8 [13.6], 56.8 [16.0], and 52.4 [13.8] mg/dl, respectively) and triglyceride level (mean [SD] level preoperatively and at 1, 3, and 5 years, 155.2 [86.1], 106.3 [45.3], 107.2 [53.4], and 126.4 [59.7] mg/dl, respectively) were significant compared with preoperative and postoperative measurements ($P < 0.001$). The decrease of low-density lipoprotein cholesterol level was significant only at 1 year ($P = 0.04$) and 3 years ($P = 0.04$) (mean [SD] level preoperatively and at 1, 3, and 5 years, 115.8 [33.2], 110.8 [32.0], 105.7 [25.9], and 110.6 [28.3] mg/dl, respectively). The changes in total cholesterol level did not reach statistical significance (mean [SD] level preoperatively and at 1, 3, and 5 years, 189.5 [38.2], 184.0 [35.4], 183.4 [31.2], and 188.1 [35.7] mg/dl, respectively). No changes in comorbidity status correlated with preoperative excess weight. Hypertriglyceridemia was the only comorbidity whose remission rates at 1 year of follow-up (partial/complete, 80.6%; complete, 72.2%) correlated with percentage of excess weight loss (76.8%) [$P = 0.005$].

Conclusions and relevance: Undergoing LSG induced efficient weight loss and a major improvement in obesity-related comorbidities, with mostly no correlation to percentage of excess weight loss. There was a significant weight regain and a decrease in remission rates of diabetes and, to a lesser extent, other comorbidities over time.

Commentaires : *Peu de travaux se sont intéressés aux résultats métaboliques à long terme (au-delà de trois ans) de la sleeve. Une méta-analyse d'études randomisées et non randomisées comparant l'efficacité de la sleeve à celle du RYGB sur la rémission du diabète de type 2 à trois ans parue récemment dans SOARD a permis de montrer que ces deux interventions faisaient jeu égal à trois ans (sleeve : 74 % vs RYGB : 81 % NS) [15]. Les auteurs rapportent ici les résultats à cinq ans de la sleeve dans une étude rétrospective (39/56 patients, 69,6 % de suivi à cinq ans). La perte d'excès de poids moyenne était de 56 % (70 % à trois ans et 77 % à un an), et l'amélioration de toutes les comorbidités, excepté l'hypertriglycémie, était indépendante de la perte pondérale. Par ailleurs, il s'agit de la première étude à rapporter une information importante, celle de la récurrence « relapse » des comorbidités et notamment du diabète après sleeve. La définition de rémission partielle du diabète choisie par les auteurs n'étant pas celle de l'ADA [3], seules les données de rémission complète (20 % à cinq ans) peuvent être comparées aux données publiées (Schauer et al., NEJM 2014 : 20 % à trois ans [16]). Dans cette étude, 50 % des patients en rémission complète à un an étaient en récurrence à cinq ans. Ces chiffres sont comparables à ceux rapportés dans le registre suédois (50 % de relapse à 10–15 ans après chirurgie bariatrique hors sleeve [7]). D'autres études sont cependant nécessaires pour confirmer cette tendance et selon des critères homogènes.*

Références

- Mingrone G, Panunzi S, De Gaetano A, et al (2015) Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet* 386:964–73
- Mingrone G, Panunzi S, De Gaetano A, et al (2012) Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 366:1577–85
- Buse JB, Caprio S, Cefalu WT, et al (2009) How do we define cure of diabetes? *Diabetes Care* 32:2133–5
- Ikramuddin S, Korner J, Lee WJ, et al (2013) Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. *JAMA* 309:2240–9
- Schauer PR, Bhatt DL, Kirwan JP, et al (2002) Bariatric surgery versus intensive medical therapy for diabetes—3-year outcomes. *N Engl J Med* 370:13–13
- Keating C, Neovius M, Sjöholm K, et al (2015) Health-care costs over 15 years after bariatric surgery for patients with different baseline glucose status: results from the Swedish Obese Subjects study. *Lancet Diabetes Endocrinol* 3:855–65
- Sjöström L (2013) Review of the key results from the Swedish Obese Subjects (SOS) trial a prospective controlled intervention study of bariatric surgery. *J Intern Med* 273:219–34
- Aron-Wisniewsky J, Clément K (2015) The gut microbiome, diet, and links to cardiometabolic and chronic disorders. *Nat Rev Nephrol* doi:10.1038/nrneph.2015.191
- Bruinsma BG, Uygun K, Yarmush ML, et al (2015) Surgical models of Roux-en-Y gastric bypass surgery and sleeve gastrectomy in rats and mice. *Nat Protoc* 10:495–507
- Rubino F, Amiel SA (2014) Is the gut the “sweet spot” for the treatment of diabetes? *Diabetes* 63:2225–8
- Zellmer JD, Mathiason MA, Kallies KJ, et al (2014) Is laparoscopic sleeve gastrectomy a lower risk bariatric procedure compared with laparoscopic Roux-en-Y gastric bypass? A meta-analysis. *Am J Surg* 208:903–10; discussion 909–10
- Chang SH, Stoll CRT, Song J, et al (2014) The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. *JAMA Surg* 149:275–87
- Lazzati A, Audureau E, Hemery F, et al (2015) Reduction in early mortality outcomes after bariatric surgery in France between 2007 and 2012: a nationwide study of 133,000 obese patients. *Surgery* doi:10.1016/j.surg.2015.08.005
- Golomb I, Ben David M, Glass A, et al (2015) Long-term metabolic effects of laparoscopic sleeve gastrectomy. *JAMA Surg* 150:1051–7
- Cho JM, Kim HJ, Menzo EL, et al (2015) Effect of sleeve gastrectomy on type 2 diabetes as an alternative treatment modality to Roux-en-Y gastric bypass: systemic review and meta-analysis. *Surg Obes Relat Dis* doi:10.1016/j.soard.2015.03.001
- Schauer PR, Bhatt DL, Kirwan JP, et al (2014) Bariatric surgery versus intensive medical therapy for diabetes — 3-year outcomes. *N Engl J Med* 370:2002–13