Bariatric Surgery in NASH

Results, indications and contra-indications

Guillaume Lassailly
CHRU de Lille
Conflit of interest

No conflict of interest related to this lecture

Contract with:
Novartis
Gilead
Bayer
Summary

A. Background of Bariatric Surgery
B. Results in NASH
C. Indications & Contra-indication
D. Risk & population
Summary

A. Background of Bariatric Surgery

B. Results in NASH

C. Indications & Contra-indication

D. Risk & population
Obesity, the « BIG » problem

Global Obesity

© Lovell Johns Ltd

% of adult population classified as obese

- 0-5%
- 5-10%
- 10-15%
- 15-20%
- 20-25%
- 25-30%
- 30-35%
- > 35%
- No Data

Source: World Health Organisation (WHO), 2012**

* An obese adult is classified as having a BMI greater than 30.
** The map uses the latest available data which varies in year of data collection.
A change of Paradigm: From malnutrition to Obesity

Global Burden Disease, Lancet 2013
Obesity, What about us?

"Un corps d’obèse est-il mort ? La seule preuve qu’il n’est pas mort, c’est qu’il grossit encore. C’est ça, la logique de l’obésité."

Une forme de vie, Amélie Notomb

Ref: Obépi 2012
Obesity and metabolic comorbidities. Data from French population

Prevalence

**HTA**

**Diabetes**

**Dyslipidemia**

<table>
<thead>
<tr>
<th>BMI</th>
<th>1 risk factor</th>
<th>2 risk factors</th>
<th>3 risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>11.2</td>
<td>11.7</td>
<td>9.7</td>
</tr>
<tr>
<td>25-30</td>
<td>12.3</td>
<td>12.0</td>
<td>10.5</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>12.8</td>
<td>12.5</td>
<td>11.0</td>
</tr>
</tbody>
</table>

Obépi 2012
Obesity, Metabolic syndrom and NAFLD

Dallas heart study

Association between BMI and Steatosis

Szczepaniak LS et al Am J Physiol Endocrinol Metabo 2005
Association between Met synd and NASH

Nice Cohort 857 (722 F/135 H) morbid obese patients (age = 40,0 ± 11,5y, BMI = 43,5 ± 5,1), referred for bariatric surgery

P<0,0001

Anty R, Personnel data
Therapeutic Strategies for obesity
Medical approach: Diet & lifestyle

In each group:
Weight 90 kg.
BMI 30 kg/m²

Between – 3 to – 5 kg after 2 year of diet and follow up

$\text{Shai I et al nejm 2008}$

6 to 17 % of patients with 10% weight loss at 2 years

$\text{Wadden et al nejm 2011}$

Benefit on cardiovascular risk?
Medical benefit of medical strategies is debated among high risk patients

Endpoint: mortality & cardiovascular morbidity

Randomised study with Type 2 diabetes patients

Hazard ratio, 0.95 (95% CI, 0.80–1.09)  
P=0.51
Weight loss and NASH

Medical strategy is beneficial in 10% of patients

Is bariatric surgery a solution?

Villar-Gomez E, Gastroenterology 2015
Efficacy of bariatric surgery on weight loss

Banding: 10-20% WL
Sleeve: 15-20% WL
Bypass: 20-35 WL

Sjöström L et al, nejm 2007
Results of bariatric surgery

Reduces overall mortality

Swedish Obese Subjects (SOS) study

Reduces CV events

Sjöström L et al, nejm 2007

Sjostrom L et al, JAMA 2012
Bariatric surgery and diabetes

Bariatric surgery improves & can induce diabetes remission at 5 year (25-45%)
Summary

A. Background of Bariatric Surgery

B. Results in NASH

C. Indications & Contra-indication

D. Risk
Evolution of histological features of NAFLD after bariatric surgery

Evolution after 1 year

Before surgery

After surgery

Ballooning Necrosis

Lobular Inflammation

Steatosis

Nafld Activity

Before surgery

After surgery

Lassailly et al, Gastroenterology 2015
Efficacy of bariatric surgery on NASH

85% of NASH disappearance

Evolution 1 year after surgery

Dixon et al, Hepatology 2004

Lassailly et al, Gastroenterology 2015
Long term evolution after bariatric surgery of NAFLD patients

Mathurin P et al, Gastroenterology 2009
Evolution of fibrosis

Improvement of fibrosis biomarkers

Klein S, Gastroenterology 2006
Evolution of fibrosis

Distribution of fibrosis stage before and one year after surgery (Metavir scale)

Improvement of fibrosis after surgery

Lassailly G, Gastroenterology 2015
What about the patients with persistent NASH at 1 year?

Comparaison of non responder vs responders patients before surgery

NR patients were more severe at baseline.

* = p<0.05

Lassailly et al, Gastroenterology 2015
What about the patients with persistent NASH at 1 year?

One year characteristics: Comparison of patients with refractory/persistent NASH at 1 year (non responders: NR) vs patients with NASH disappearance (Responders: N):

---

Weight loss

**ΔBMI**

![Box plot showing ΔBMI comparison between Responders (R) and Non-Responders (NR).](image)

- **NR**
  - Max: 35
  - Min: -5

- **R**
  - Max: 35
  - Min: -5

**Insulin Resistance Index**

![Box plot showing 1/QUICKI comparison between Responders (R) and Non-Responders (NR).](image)

- **NR**
  - Max: 5.5
  - Min: 2

- **R**
  - Max: 5.5
  - Min: 2

---

*Lassailly et al, Gastroenterology 2015*
How does it work?
Steatosis & insulin resistance: Association before and after surgery

IR is improved after surgery

Histology is associated to IR profile before and after surgery
Steatosis & insulin resistance

NAFLD and its severity are associated to IR

Glucose => ↑ lipogenesis => ↑ steatosis => ↑ IR
↓ Glc => lipolysis => ↓ steatosis => ↓ IR

Perry R et al, Nature 2014
## Optimizing gut hormones

<table>
<thead>
<tr>
<th>Gut hormones</th>
<th>After Bariatric surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1</td>
<td>↑</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>↓ (sleeve)</td>
</tr>
<tr>
<td>PYY</td>
<td>↑</td>
</tr>
<tr>
<td>PP</td>
<td>↑</td>
</tr>
<tr>
<td>Oxyntomodulin</td>
<td>↑</td>
</tr>
</tbody>
</table>

Improves: IR  
Changes in appetite and taste  
Gut microbiota

Acosta A et al, Gut 2014; Lassailly G et al, J Hepatol 2013
Appetite and satiety are controlled by the hypothalamus in relation with the limbic system (emotion & reward area).

### Gut-brain Axis

<table>
<thead>
<tr>
<th>Orexigene Hormone</th>
<th>Anorexigene Hormones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghreline</td>
<td>PYY</td>
</tr>
<tr>
<td></td>
<td>GLP-1</td>
</tr>
<tr>
<td></td>
<td>Cholécystokine</td>
</tr>
</tbody>
</table>

Gut hormones:
- PYY
- Oxytomodulin
- GLP-1
- Leptin
- Insulin/glucagon

Vagual nerve*
Changing eating behavior

Time 1: 6 week after surgery
Time 2: 8 month

Van Vuuren MAJ et al., Obes Surg 2017
Change in gut microbiota

Liou AP, Sci Trans Med 2013
Summary

A. Background of Bariatric Surgery

B. Results in NASH

C. Indications & Contra-indication

D. Risk & population

What are saying health authorities and experts?
# Current validated indications

<table>
<thead>
<tr>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>- BMI &gt; 40 kg/m²</td>
</tr>
<tr>
<td>- BMI &gt; 35 kg/m² with at least one complication secondary to severe obesity</td>
</tr>
<tr>
<td>- Cardiovascular disease</td>
</tr>
<tr>
<td>- Sleep Apnea</td>
</tr>
<tr>
<td>- Type 2 diabetes</td>
</tr>
<tr>
<td>- NASH (in France, HAS recommendation 2009)</td>
</tr>
</tbody>
</table>

**HAS 2009:** No recommendation for the BMI between 30 and 35 kg/m².  
**FDA:** gastric Banding if  
- BMI > 40 kg/m²  
- Or BMI > 30 kg/m² with:  
  - HTA  
  - Sleep apnea  
  - Diabète
## Current validated contra-indications

<table>
<thead>
<tr>
<th>Contra-indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol &gt; 20g/j for women and 30g/j for men</td>
</tr>
<tr>
<td>Presence of <em>Helicobacter pylori</em> resistant to medical therapy</td>
</tr>
<tr>
<td>Gastric or duodenal Ulcer in the past 2 month</td>
</tr>
<tr>
<td>Gastric Dysplasia or history of gastric cancer</td>
</tr>
<tr>
<td>Gastroesophageal reflux resistant to treatment (for sleeve gastrectomy)</td>
</tr>
<tr>
<td>Chronic Diarrhea</td>
</tr>
<tr>
<td>Eating disorders (according to DSM V)</td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
</tr>
<tr>
<td>Severe Mental diseases</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
</tr>
<tr>
<td>Disease related to short term life threatening or anaesthesiological contra-indications</td>
</tr>
</tbody>
</table>
As procedures are increasing, should we propose surgery to all our patients?

In France, 1% of potential candidates have performed surgery.
Bariatric surgery: The treatment for NASH?

NAFLD (Non alcoholic fatty liver disease)

Normal liver

Steatosis

Steato hepatitis (NASH)

Cirrhosis
Summary

A. Background of Bariatric Surgery

B. Results in NASH

C. Indications & Contra-indication

D. Risk & population

Should we extented the indication of bariatric surgery to all NASH patient?
### Clinical data

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>No complications</th>
<th>Complications</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean ± SD</td>
<td>40,9 ± 11,7</td>
<td>42,9 ± 10,1</td>
<td>&lt; 0,01</td>
</tr>
<tr>
<td>BMI mean ± SD</td>
<td>47,2 ± 9,1</td>
<td>50,5 ± 7,2</td>
<td>&lt; 0,01</td>
</tr>
<tr>
<td>Gender, % (M)</td>
<td>23,9</td>
<td>27,9</td>
<td>0,18</td>
</tr>
</tbody>
</table>

### Cardiovascular Risk

<table>
<thead>
<tr>
<th></th>
<th>No complications</th>
<th>Complications</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTA, %</td>
<td>56,6</td>
<td>61,8</td>
<td>0,14</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>29,8</td>
<td>35,2</td>
<td>0,12</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>57</td>
<td>61,3</td>
<td>0,18</td>
</tr>
</tbody>
</table>

### Histology

<table>
<thead>
<tr>
<th></th>
<th>No complications</th>
<th>Complications</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis</td>
<td>0,32 ± 0,7</td>
<td>0,52 ± 0,9</td>
<td>&lt; 0,01</td>
</tr>
<tr>
<td>≥ F2 (METAVIR), %</td>
<td>5,9</td>
<td>11,2</td>
<td>&lt; 0,01</td>
</tr>
<tr>
<td>Steatosis, % (median)</td>
<td>25</td>
<td>30</td>
<td>&lt; 0,01</td>
</tr>
<tr>
<td>NAS</td>
<td>1,8 ± 1,5</td>
<td>2 ± 1,5</td>
<td>0,054</td>
</tr>
</tbody>
</table>

Lassailly G, Lille, AASLD 2016, Abs. 1090
NASH does not increase the risk of complications of bariatric surgery.
Morbidity, multivariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02</td>
<td>1.003-1.3</td>
<td>0.012</td>
</tr>
<tr>
<td>BMI</td>
<td>1.04</td>
<td>1.02-1.06</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fibrosis ≥ F2</td>
<td>1.90</td>
<td>1.16-3.11</td>
<td>0.010</td>
</tr>
<tr>
<td>Steatosis ≥ 30 %</td>
<td>1.54</td>
<td>1.15-2.08</td>
<td>0.004</td>
</tr>
</tbody>
</table>

- Post-op morbidity is linked to: age and to the severity of fibrosis, steatosis and BMI
- Infection was the most common (severe) complication
Fibrosis, independant factor of complications

What about cirrhosis?
Data in cirrhotic patients


• Mortality of compensated cirrhosis (N=3888):
  • 0.9% vs 0.3%
  • increased risk x 2-3

• Mortality of decompensated cirrhosis (N=62):
  • 16.3% vs 0.3%
  • Increased risk x 21

Mosko JD et al Clin Gastroenterol Hepatol, 2011

Retrospective monocentric study:
  2119 patients opérés: Gastric Bypass
  N= 30 cirrhosis
    BMI: 50 vs 48 kg/m²
    Gender ratio 1.3
    Diabetes: 70 vs 21%
  Diagnosis of cirrhosis was performed during the procedure in 90% des cas 30% of morbidity, but no decompensation, no death at 1 year.

Dallal RM et al, Obes Surg 2004
## Data in cirrhotic patients

<table>
<thead>
<tr>
<th></th>
<th>Cirrhosis N = 21</th>
<th>No cirrhosis N = 1020</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI kg/m²</td>
<td>48.7</td>
<td>47.1</td>
<td>ns (0.14)</td>
</tr>
<tr>
<td>age</td>
<td>48</td>
<td>41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ASA (score)</td>
<td>3</td>
<td>2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bilirubin mg/L</td>
<td>7</td>
<td>4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AST UI/L</td>
<td>44</td>
<td>22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>3.5</td>
<td>3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Platelets/ mm³</td>
<td>175 000</td>
<td>210 000</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TP</td>
<td>91%</td>
<td>100%</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Lassailly et al, AASLD, 2013
# Data in cirrhotic patients

<table>
<thead>
<tr>
<th></th>
<th>Before surgery</th>
<th>1 year after</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI kg/m²</td>
<td>48.7</td>
<td>40.7</td>
<td>0.0002</td>
</tr>
<tr>
<td>Bilirubin mg/L</td>
<td>7</td>
<td>6.1</td>
<td>ns (0.22)</td>
</tr>
<tr>
<td>TP</td>
<td>91%</td>
<td>87%</td>
<td>ns (0.32)</td>
</tr>
<tr>
<td>ALT UI/L</td>
<td>38</td>
<td>25</td>
<td>0.007</td>
</tr>
<tr>
<td>AST UI/L</td>
<td>44</td>
<td>29</td>
<td>0.007</td>
</tr>
<tr>
<td>GGT UI/L</td>
<td>112 UI/L</td>
<td>58</td>
<td>0.02</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.25 %</td>
<td>5.6%</td>
<td>0.0006</td>
</tr>
<tr>
<td>Fasting Glc mmol/L</td>
<td>7.43</td>
<td>5.2</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Lassailly et al, AASLD, 2013
Data in cirrhotic patients

<table>
<thead>
<tr>
<th></th>
<th>before</th>
<th>1 year after surgery</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis</td>
<td>3.9</td>
<td>3.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Steatosis</td>
<td>50%</td>
<td>10%</td>
<td>0.01</td>
</tr>
<tr>
<td>Ballooning</td>
<td>1</td>
<td>0</td>
<td>ns (0.9)</td>
</tr>
<tr>
<td>inflammation</td>
<td>1</td>
<td>0.5</td>
<td>ns (0.3)</td>
</tr>
<tr>
<td>NAS</td>
<td>4</td>
<td>2.5</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Staff decision before surgery.
Before surgery: CT scan, Hepatic veinous pressure gradient, CPT A

Lassailly et al, AASLD, 2013
## Efficiency and cost-efficiency of bariatric surgery in NASH

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cost (USD)</th>
<th>Weight</th>
<th>Benefit (USD)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe obesity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>$22,406</td>
<td>10.075</td>
<td>29.253</td>
<td>—</td>
</tr>
<tr>
<td>ILI: F3 only</td>
<td>$23,263</td>
<td>10.104</td>
<td>29.355</td>
<td>Dominated</td>
</tr>
<tr>
<td>ILI: F2+</td>
<td>$24,761</td>
<td>10.119</td>
<td>29.417</td>
<td>Dominated</td>
</tr>
<tr>
<td>ILI: F1+</td>
<td>$26,852</td>
<td>10.132</td>
<td>29.469</td>
<td>Dominated</td>
</tr>
<tr>
<td>ILI: All</td>
<td>$27,608</td>
<td>10.131</td>
<td>29.462</td>
<td>Dominated</td>
</tr>
<tr>
<td>Surgery: F3 only</td>
<td>$27,795</td>
<td>10.509</td>
<td>30.299</td>
<td>$12,439</td>
</tr>
<tr>
<td>Surgery: F2+</td>
<td>$36,347</td>
<td>10.936</td>
<td>31.142</td>
<td>Dominated</td>
</tr>
<tr>
<td>Surgery: F1+</td>
<td>$47,424</td>
<td>11.516</td>
<td>32.200</td>
<td>Dominated</td>
</tr>
<tr>
<td>Surgery: All</td>
<td>$51,565</td>
<td>11.745</td>
<td>32.595</td>
<td>$19,222</td>
</tr>
</tbody>
</table>

Most benefit appears in the most severe patients

---

*Klebanoff MJ, Hepatology 2016*
Which procedure should be proposed?

We may have to adjust the gastric band a little.
Bypass or gastric band?

**TABLE 2. Multivariate Analysis of Predictive Factors of Steatosis and NAS 5 Years After AGB and RYGB (Step-by-Step Linear Regression Model)**

<table>
<thead>
<tr>
<th></th>
<th>Steatosis, %</th>
<th>NAS</th>
<th></th>
<th>Relative Contribution, %</th>
<th>Relative Contribution, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>P</em></td>
<td></td>
<td><em>P</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline value</td>
<td>&lt;0.001</td>
<td>32.9</td>
<td>&lt;0.001</td>
<td>32.6</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>&lt;0.001</td>
<td>60.1</td>
<td>&lt;0.001</td>
<td>57.2</td>
<td></td>
</tr>
<tr>
<td>RYGB</td>
<td>0.007</td>
<td>4.6</td>
<td>0.044</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>T2DM</td>
<td>0.054</td>
<td>2.4</td>
<td>0.001</td>
<td>7.5</td>
<td></td>
</tr>
</tbody>
</table>

Caiazzo R et al, Annals of Surgery 2014
Conclusion

• Bariatric surgery is efficient in NASH and should be second choice strategy in morbid and a severe obese patient with NASH

• Many questions remain:
  • What is the long term effect?
  • Is surgery suitable for NASH with BMI < 35 kg/m²? Only for F3 NASH patients?
  • Surgery in cirrhotic patients is contra-indicated. However, it should be evaluated in highly compensated patient without other therapeutic options.
Dankjewel, Merci

“A boy? I thought you were having a gastric bypass.”