“Metabolic effect of bariatric surgery: Is there a role for gut microbiota?”

Dr Judith Aron-Wisnewsky
MD-PHD Nutrition

ICAN Institute Cardiométabolisme et Nutrition
Inserm U872  NutriOmique
University Pierre & Marie Curie/Paris 6
Pitié-Salpêtrière, hospital Paris

3rd october 2017
Presentation work flow

• I- Microbiota and obesity
  • Diversity in overweight
  • Diversity in morbid obesity

• II- Bariatric surgery
  • Metabolic effects
  • Microbiota effects

• III- Bariatric surgery and metabolic outcomes: role of gut microbiota
  • Diversity changes
  • Ecosystem Modulation
  • Differences between surgical technics
I Microbiota dysbiosis, obesity and metabolism

** METAHIT **
- 292 subjects
- Lean-overweight obese

** Micro-Obese **
- 49 subjects
- Overweight and obese

** LGC (23%) **  
- t0
- Bact.
- Rum.
- Prev.

** HGC (77%) **
- "Pro-inflammatory"
- "Anti-inflammatory"

LGC
- ↑ total adiposity
- ↑ insulin resistance
- ↑ Dyslipidemia
- ↑ inflammation (systemic and WAT)

Concordant with previous data Turnbaugh Nature 2009, Yatsunenko et al; Nature 2012
I bacterial diversity (overweight and moderate obesity)

Dietary interventions ++

Massive obesity

Moderate obesity

Overweight

Lean

predisposing factor

Constitution

exacerbation

Chronicisation

Complications
I Microbaria research protocol (2 # surgeries)

Baseline Check-up

Bariatric Surgery

Times of follow-up after surgical weight loss intervention

M1  M3  M6  1 year

Surgical samples

Adipose tissue analysis

Liver

Intestine

AT

Detailed clinical phenotyping

Bio-clinical, anthropometric and sociodemographic data

Bioresoucres biobanking: serum, plasma, PBMC, urine, DNA, feces...

Body composition (DXA, DER)

Dietary and self – administred questionnaires

Serum Metabolomic analysis

Feces Metagenomic analysis
I Microbaria research protocol (2 # surgeries)

Times of follow-up after surgical weight loss intervention

- M1
- M3
- M6
- 1 year

Detailed clinical phenotyping

- Dietary and self-administered questionnaires
- Body composition (DXA, DER)
- Detailed clinical phenotyping
- Biospecimen collection: Serum, plasma, PBMC, urine, DNA, feces

Baseline Check-up

Serum Metabolomic analysis
Feces Metagenomic analysis
Candidats to bariatric surgery
Massive obesity : BMI = 45kg/m²

 ↗ Prevalence of LGC patients

**Characteristics of LGC patients:**

**Confirmation:**
 ↗ Triglycerides *
 ↗ Insulin resistance *
 ↗ Systemic inflammation (fibrinogen, neutrophil count) *

Despite same overall BMI

**Characteristics of LGC patients:**

**New findings:**
 ↗ Fat trunk mass (DXA)
 ↗ DT2
 ↗ HTA and severity (as seen with Nº drugs)
 ↗ Obstructive Sleep Apnea

Despite same overall BMI

Aron-wisnewsky J, Prifti E, Clement K
Gene richness associates negatively with BMI but also adverse body composition (↑ fat mass, ↑ fat mass trunk, ↓ fat free mass) and ↑ adipocyte volume. And ↑ insulin resistance.
**II weight loss interventions?**

- **Diet interventions ++**
- **Massive obesity**
- **Moderate obesity**
- **Overweight**
- **Lean**

**Constitution**

**Exacerbation**

**Chronicisation**

**Complications**

**Surgery Intervention/ diet**

- Furet et al, Diabetes, 2010
- Kong, Plos One, 2014
- Magalhaes I, JCI, 2015
- Monteiro-Sepulveda M, Cell Metab 2015

**Years**

**Weight**

**Cotillard A, Nature, 2013**

**Kong LC, AM J Clin Nut 2013**

**Kong, Plos one 2014**

**Aron, AM J Clin Nutr 2013**

**Kong, Plos One, 2014**

**Aron-Wisnewsky J, Curr Atheros Rep et al 2014**

**Monteiro-Sepulveda M, Cell Metab 2015**
Presentation work flow

• I- Microbiota and obesity
  • Diversity in overweight
  • Diversity in morbid obesity

• II- Bariatric surgery
  • Metabolic effects
  • Microbiota effects

• III- Bariatric surgery and metabolic outcomes: role of gut microbiota
  • Diversity changes
  • Ecosystem Modulation
  • Differences between surgical technics
II bariatric surgery interventions

Adjustable gastric banding

Sleeve

Roux-en-Y bypass

Aron et al. Nature gastro review 2012
II bariatric surgery interventions

- Major and sustained weight loss in the long term
- Metabolic improvement (T2D remission++)
- Systemic and adipose tissue inflammation improvement

II Digestive tract and bariatric surgery

Small intestine: duodenum, jejunum
Pancreatic enzymes, bicarbonate, bile salts
pH 5.7–6.4
$10^3$–$10^4$ bacteria/ml
Lactobacillus
Escherichia coli
Enterococcus faecalis

Stomach
Acid production, pepsin, amylase
pH 1–2
<10³ bacteria/ml
Lactobacillus
Streptococci

Large intestine: caecum, colon
Bicarbonate, mucus
pH 5.7–6.8
$10^{12}$ bacteria/ml
Bacteroidetes
Eubacterium
Bifidobacterium
Ruminococcus
Pepstreptococcus
Propionibacterium
Clostridium
Lactobacillus
Escherichia
Streptococci

Aron-wisnewsky et al; Nature reviews gastro 2012
II-1 Bariatric surgery and microbiota changes

Aron-wisnewsky, doré, Clement, Nature reviews gastro 2012
II-1 Bariatric surgery and microbiota: phenotype transfert

Post-GBP transfert de flore

Gut microbiota transfert mimick bariatric surgery effects

Liou et al Sci Transl Med 2013
Presentation work flow

• I- Microbiota and obesity
  • Diversity in overweight
  • Diversity in morbid obesity

• II- Bariatric surgery
  • Metabolic effects
  • Microbiota effects

• III- Bariatric surgery and metabolic outcomes: role of gut microbiota
  • Diversity changes
  • Ecosystem Modulation
  • Differences between surgical technics
III-1 Microbial richness after RYGB

Gene richness 3 and 6 months after surgery (16S)

N= 30 massively obese individuals

Kong et al Am J Clin Nut 2013
III-1 Microbial richness after RYGB

Gene richness at 3 and 12M after surgery (shotgun) but did not reach significance

N=13 baseline massively obese individuals
N=8 at M12

Pallega et al Genom medecin 2016
Presentation work flow

I- Microbiota and obesity
   • Diversity in overweight
   • Diversity in morbid obesity

II- Bariatric surgery
   • Metabolic effects
   • Microbiota effects

III- Bariatric surgery and metabolic outcomes: role of gut microbiota
   • Diversity changes
   • Ecosystem Modulation
   • Differences between surgical technics
III-2 RYGB and microbial composition changes

3 patients per groups, non paired, 16S

• Obesity
  ⇒ Increase in energy extraction from food

• RYGB
  • Increase in anaerobic bacteria
    (Gammaproteobacteria, 89% enterobacteria)
  • Decrease in Firmicutes & and methanogens

6 patients DT2, metagenomic

• Decrease in Firmicutes
• Increase in proteobacteria

### III-2 patient’s Characteristics

30 obeses, (27 women), 7 type-2 diabetic patients

<table>
<thead>
<tr>
<th></th>
<th>Before bypass</th>
<th>Controls (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>126 ± 4.2^A</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>47.6 ± 1.5^A</td>
<td></td>
</tr>
<tr>
<td>Adipocyte diameter (µm)</td>
<td>116.7 ± 1.5^A</td>
<td></td>
</tr>
<tr>
<td>REE (kcal)</td>
<td>1,814.4 ± 54.8^A</td>
<td></td>
</tr>
<tr>
<td>Fat mass %</td>
<td>47.9 ± 1.0^A</td>
<td></td>
</tr>
<tr>
<td>Fat-free mass %</td>
<td>50.0 ± 1.0^A</td>
<td></td>
</tr>
<tr>
<td>Glycemia (mmol/l)</td>
<td>6.4 ± 0.5^A</td>
<td></td>
</tr>
<tr>
<td>A1C (%)</td>
<td>6.4 ± 0.3^A</td>
<td></td>
</tr>
<tr>
<td>Insulinemia (µU/ml)</td>
<td>17.1 ± 1.6^A</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.88 ± 0.09^A</td>
<td></td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>6.4 ± 0.5^A</td>
<td></td>
</tr>
<tr>
<td>Plasma lipid homeostasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.54 ± 0.16^A</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.57 ± 0.19^A</td>
<td></td>
</tr>
<tr>
<td>Plasma hs-CRP (mg/dl)</td>
<td>3.1 ± 0.8^A</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>36 ± 3</td>
<td></td>
</tr>
<tr>
<td>Sexe</td>
<td>13 F</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.7 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Glycemia (mmol/l)</td>
<td>4.3 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Insulinemia (µU/ml)</td>
<td>3.8 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>0.8 ± 0.1</td>
<td></td>
</tr>
</tbody>
</table>

**Suivi en basal, 3 et 6 mois après la chirurgie**
Selles à chaque temps
Méthodes RT-PCR

_Furet et al, Diabetes 2010_
III-2 patient’s Characteristics

- Calories (kcal)
  -50%

- Leptine (ng/ml)
  -50%

- Poids (kg)
  -22%

Glycemie à jeun (mmol/l)

hsCRP (mg/dl)

Furet et al, Diabetes 2010

Paired Wilcoxon ; * p<0.05 vs M0 ; * M3 vs. M6
III-2: Evolution post-RYGB: Bacteroides/Prevotella

- Ratio Bacteroides/Prevotella is decreased in obese compared to controls.
- Increase after surgery.

Changes is negatively associated with BMI, fat mass and leptin.

Changes negatively associates with BMI, fat mass and leptin
\((R -0.53 \ p < 0.001)\)

Persists after adjustment for calory intake.

Yet depend on food intake.

Furet et al, Diabetes 2010
F. prausnitzii is decreased in T2D patients and increase after surgery. Changes correlates negatively with inflammatory parameters. Dependant on food intake.

Furet et al, Diabetes 2010
III-3 14 species differ

Kong et al, AJCN 2013
III-3 14 species differ

Changes in microbiota correlated with food intake markers and corpulence parameters

After adjustment for food intake only 50% of the associations remained significant
III-2 Links with host metabolism (the adipose tissue)

Decrease in inflammatory gene expression and increase in extra cellular matrix genes

Microarray: gene expression

Pyrosequençage

Kong et al, AJCN 2013
Increase in the number of association between host and gut microbiota post-RYGB

Clinical improvement
- Increase in diversity
- Increase in anti-inflammatory bacteria

Restore the cross talk between host and microbiota

**Presentation work flow**

- **I- Microbiota and obesity**
  - Diversity in overweight
  - Diversity in morbid obesity

- **II- Bariatric surgery**
  - Metabolic effects
  - Microbiota effects

- **III- Bariatric surgery and metabolic outcomes: role of gut microbiota**
  - Diversity changes
  - **Ecosystem Modulation : akkermansia ?**
  - Differences between surgical technics
III.3- Akkermansia, metabolic alterations

Microobese study: 49 overweight or obese patients (without DT2)

Akkermansia muciniphila is associated with insulin sensitivity in mice


High Akk associates with better insulin sensibility

Akk is a SCFA producer

Significant positive correlation between Akk and acetate levels

Dao et al; Gut 2015
I- Microbiota and obesity
   • Diversity in overweight
   • Diversity in morbid obesity

II- Bariatric surgery
   • Metabolic effects
   • Microbiota effects

III- Bariatric surgery and metabolic outcomes: role of gut microbiota
   • Diversity changes
   • Ecosystem Modulation: proteobacteria?
   • Differences between surgical technics
III-3 microbiota modulation and clinical phenotype

Commun result after all studies involving RYGB
At short, mid and long term in mice and in humans

Increase in Gammaproteobacteria and proteobacteria +++

Correlation between levels of gammaproteobacteria and weight post surgery

III-3 long term changes after bariatric surgery

Différence entre patients obèses et BPG
Gammaproteobacteries +++

Effets long terme maintenus

Gammaproteobacteries

Tremaroli et al Cell metab 2015
III-3 microbiota modulation and clinical phenotype

Weight loss
Decreased energy storage

Metabolic effects
Satiety, energy metabolism
Insulin sensitivity

ʤ Respiratory quotient (night)

ʤ SCFA post RYGB
ʤ BCFA

ʤ bile acid pool
ʤ FGF19 (post prandial)

ʤ sugar utilisation
ʤ lipid utilisation

Tremaroli et al Cell metab 2015;
III.3- microbiota modification and clinical outcomes

Aron-Wisnewsky, Clement, Curr Atheroscler Rep 2014
III.9- Differences between BS microbiota modulation

Major difference between bypass and the other two (not so different between sleeve and sham)

Major Differences between surgical models

Zucker rats

Human randomised study (n=14): changes in microbiota composition and function are more important after RYGB than sleeve

Conclusion 2

- Furet et al, Diabetes, 2010
- Kong, Plos One, 2014
- Aron-wisnewsky, Clement Nature review nephrology 2015
- Magalhaes I, JCI, 2015
- Monteiro-Sepulveda M, Cell Metab 2015

Chirurgie bariatrique (PHRC)

Increase in gene richness at 3-6 months (16S)

At T 12M (metagenomic)

Adatation (short and longer term)

⇒ Enterobacteria:

Bacterial groups associated with improvement in metabolic and inflammatory parameters (50% dépendent on food intake)

Associations with adipose tissue

Restauration du dialogue inter-organe
Conclusions

Diversity is reduced in overweight to massive obesity associated with metabolic complications

Interventions can modulate microbiota and have a link on insulin sensitivity

50% of clinical improvement related with microbiota depend on food intake

Interventions modify signature and apparently for long term

Yet is it the same evolution for patients that regain weight? Or do not present with diabetes remission

These modifications are partly responsible for weight loss