

CHANGES IN INCRETINS BILE ACIDS AND THE MICROBIOME AFTER DUODENAL MUCOSAL RESURFACING IN PATIENTS WITH TYPE 2 DIABETES.

S. Meiring, A.C.G. van Baar, E. Meessen, M.R.
Soeters, F. Holleman, A.K. Groen, M. Nieuwdorp,
J.J.G.H.M. Bergman



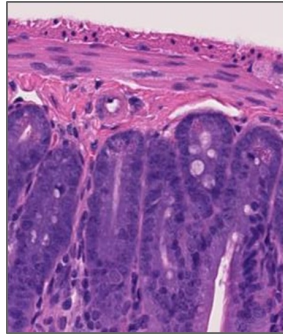
@DDWMeeting | #DDW2021

Disclosure of Conflicts of Interest

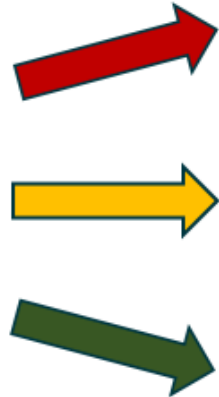
I herewith declare the following paid or unpaid consultancies, business interests or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

Unrestricted grant for investigator initiated DMR studies. Participated in sponsor-initiated studies by Fractyl in the use of DMR in T2D

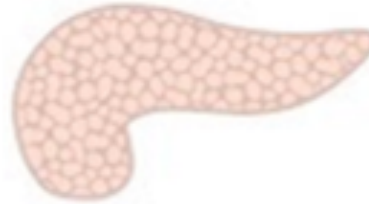
Target the duodenum for treatment of T2D



Duodenum



Pancreas

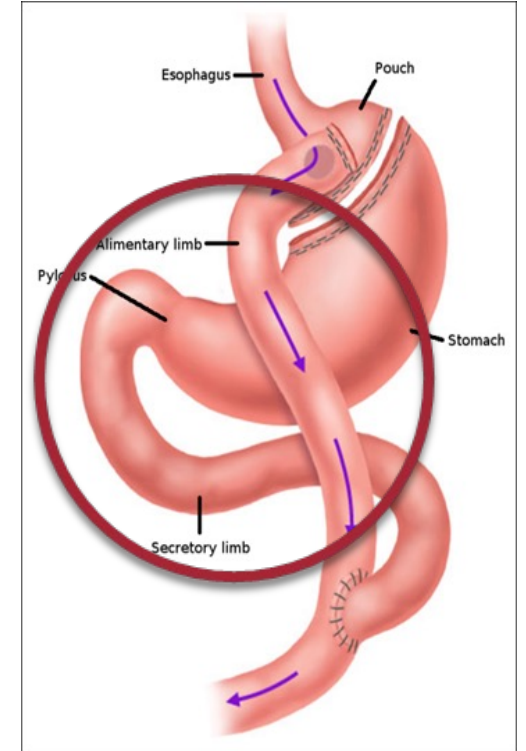


Liver



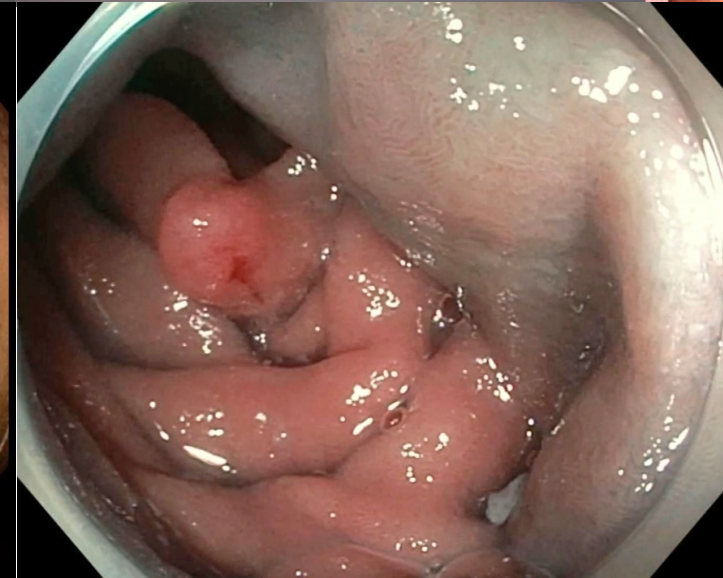
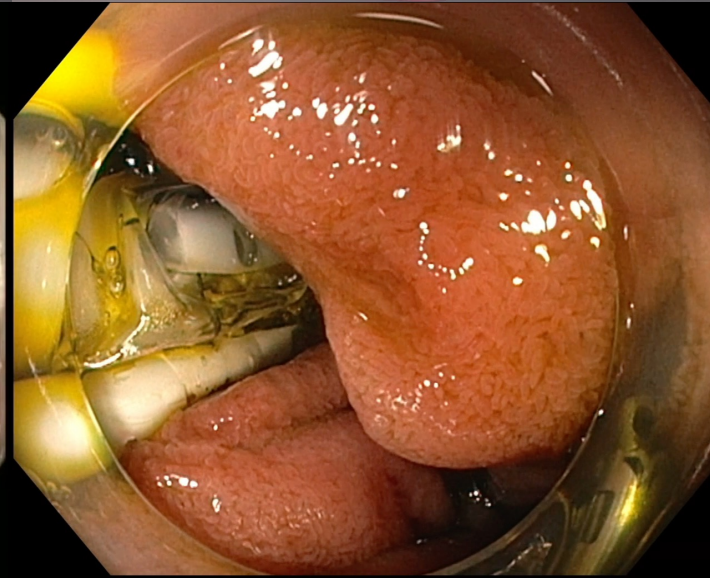
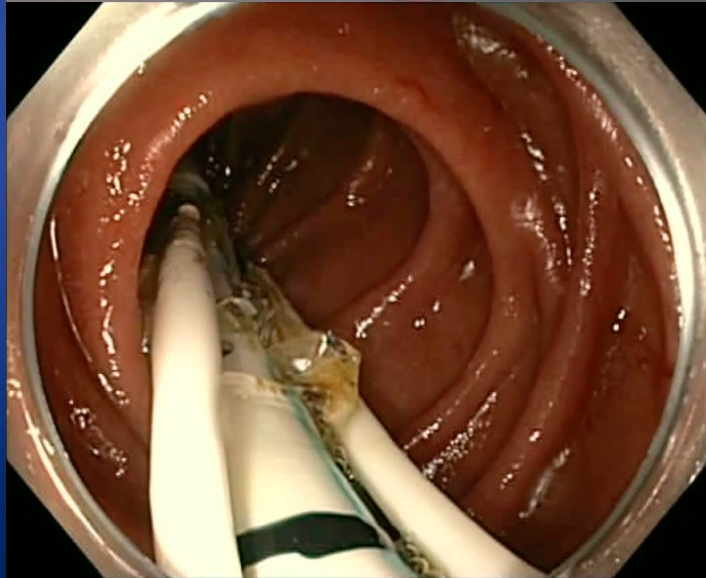
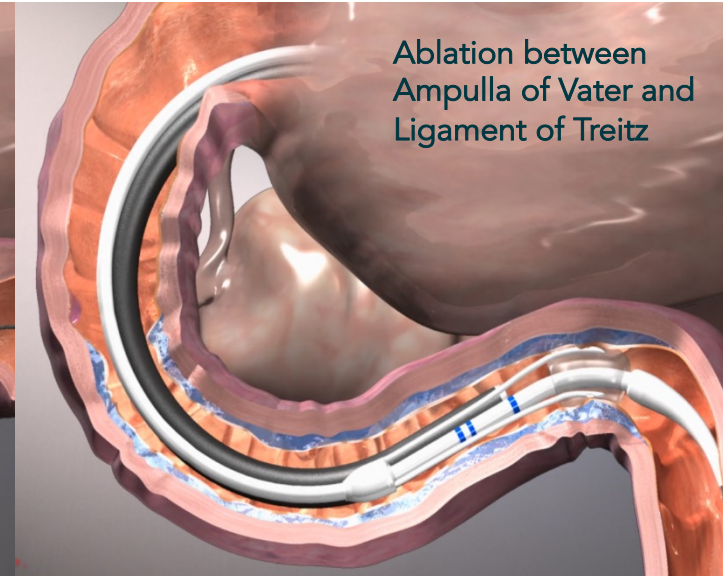
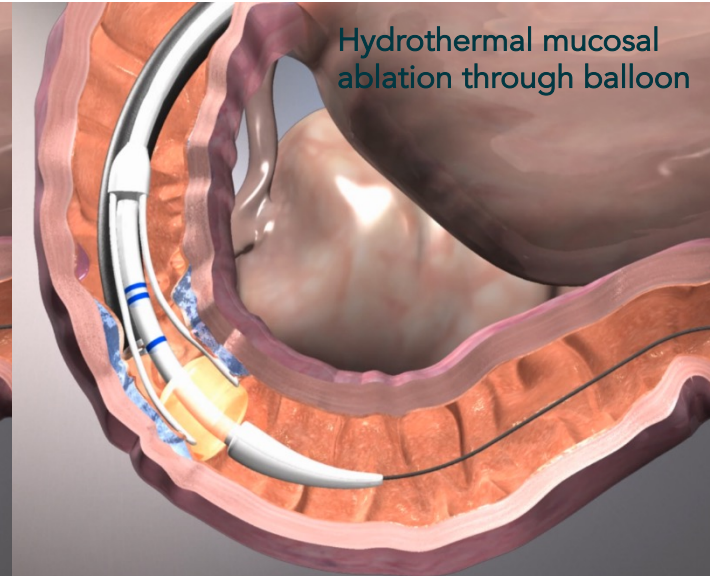
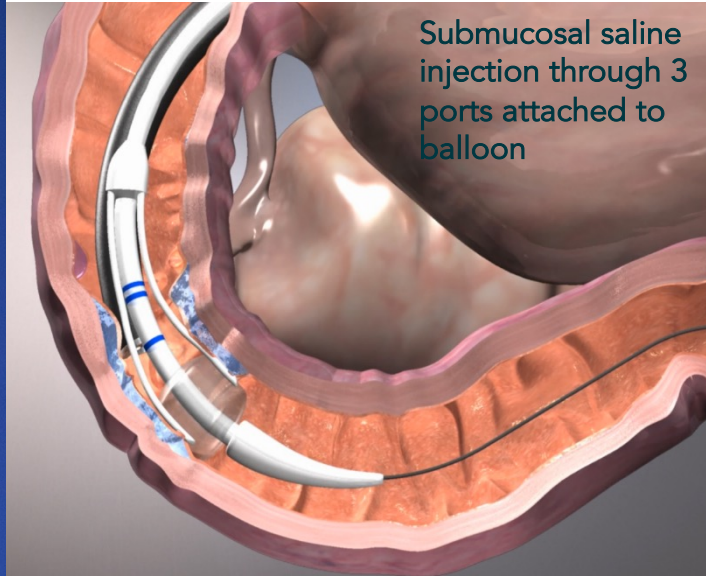
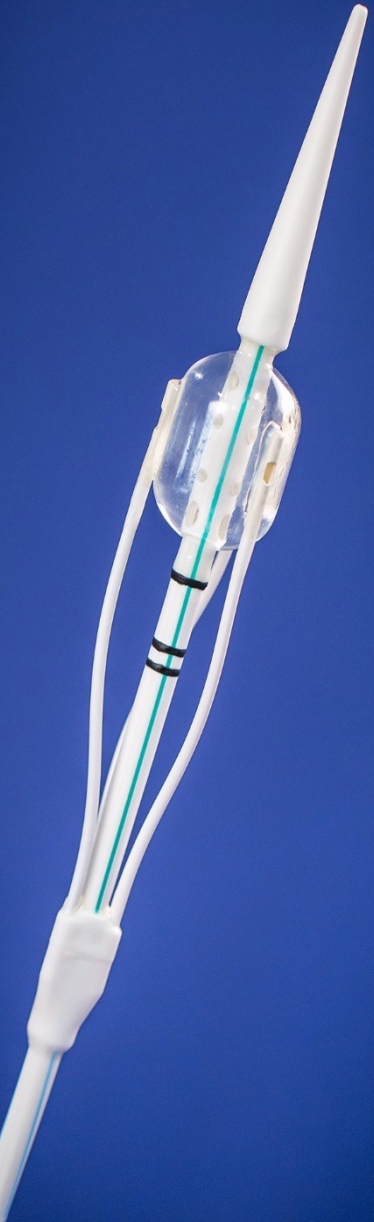
“Westernized” diet causes changes in entero-endocrine signalling

Insulin resistance and eventually Type 2 Diabetes



Bariatric surgery improves insulin resistance via bypassing duodenum

Revita™ Duodenal Mucosal Resurfacing Procedure



INSPIRE study

- **Single arm, single center, open-label**
 - Amsterdam UMC
 - 16 patients with type 2 diabetes, basal insulin

- **Intervention:**

- 1. DMR procedure**

- Insulin stopped at day of DMR
- 2 weeks post-procedural diet

- 2. GLP-1 RA (Victoza, liraglutide)**

- Started 2 weeks after DMR
- Stepwise dose increase to 1.8mg/day

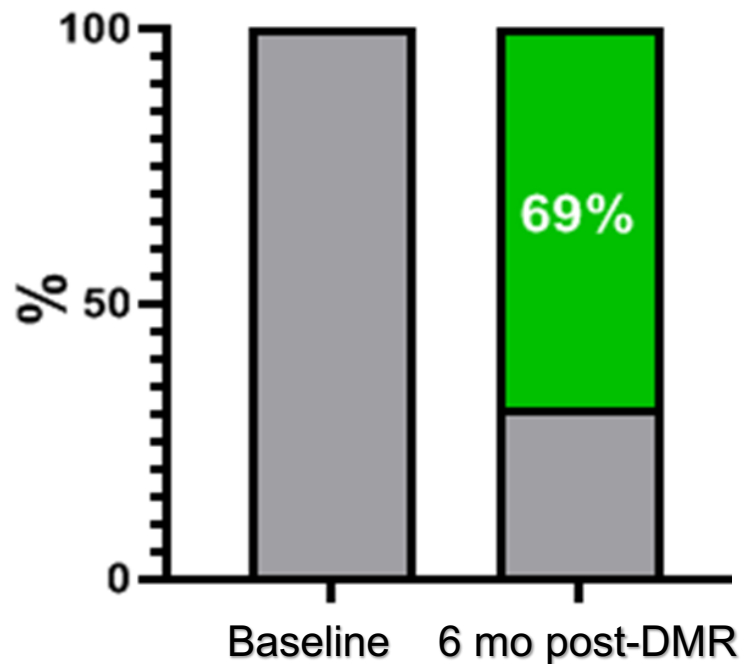
INSPIRE study

- **Single arm, single center, open-label**
 - Amsterdam UMC
 - 16 patients with type 2 diabetes, basal insulin
- **Endpoints**
 - % pts without insulin & HbA1c ≤ 59 mmol/mol
 - Glycaemic and metabolic parameters

- **Intervention:**
 1. **DMR procedure**
 - Insulin stopped at day of DMR
 - 2 weeks post-procedural diet
 2. **GLP-1 RA (Victoza, liraglutide)**
 - Started 2 weeks after DMR
 - Stepwise dose increase to 1.8mg/day

69% off insulin while improving metabolic health

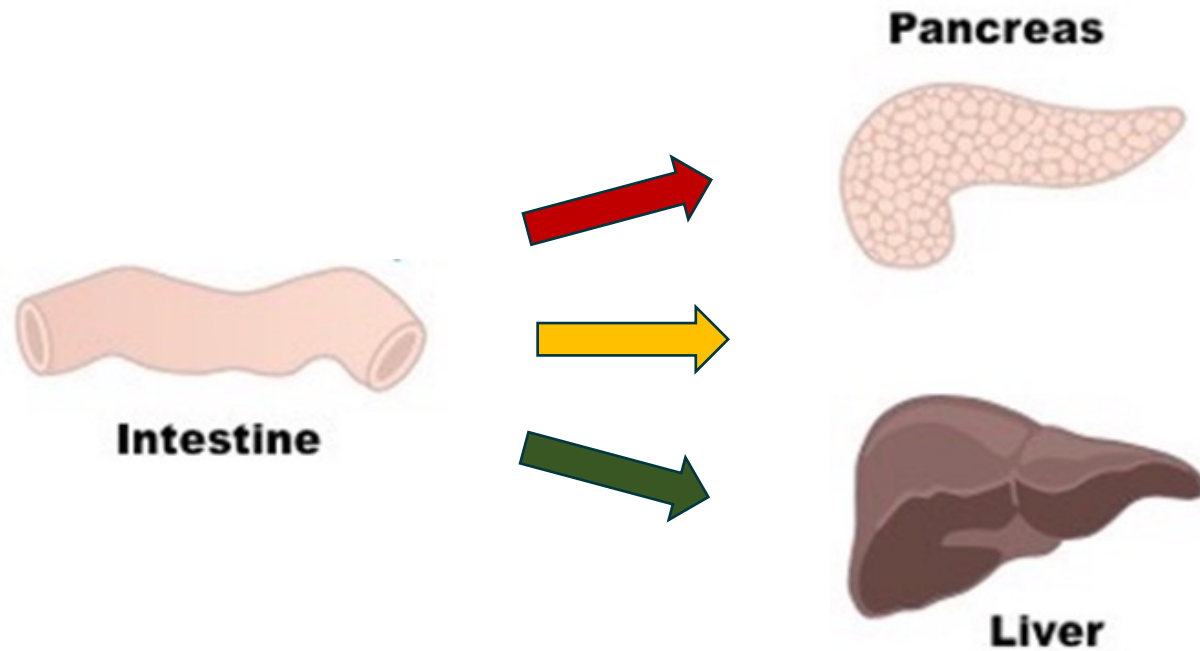
% off insulin with HbA1c < 59 mmol/mol



	Baseline	6 mo (n=16)	
HbA1c [%]	7.5	7.0	<i>p=0.18</i>
HOMA-IR	8.4	2.5	<i>p=0.002</i>
Fasting Glucose	10.1	8.0	<i>p=0.039</i>

Body Mass Index	28.8	26.5	<i>p=0.001</i>
Liver fat [%]	8.1	5.3	<i>p=0.053</i>

How does DMR improve metabolic health?

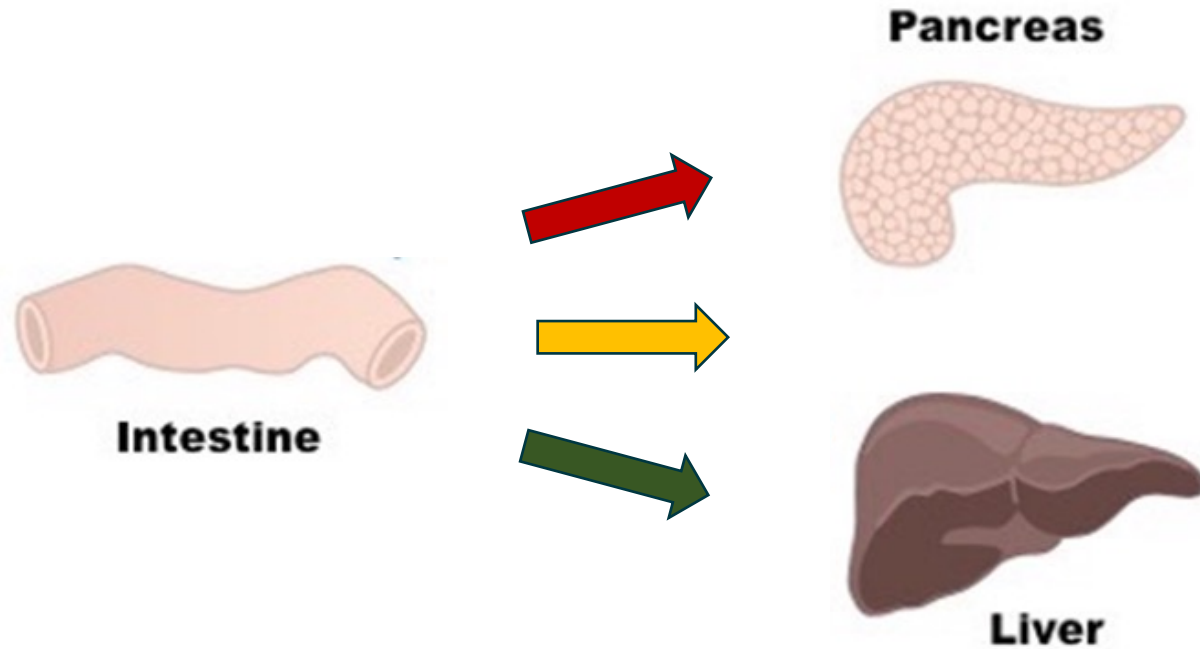


1. Incretins (GLP-1 + GIP)

2. Bile Acids

3. Microbiome

How did we investigate this?



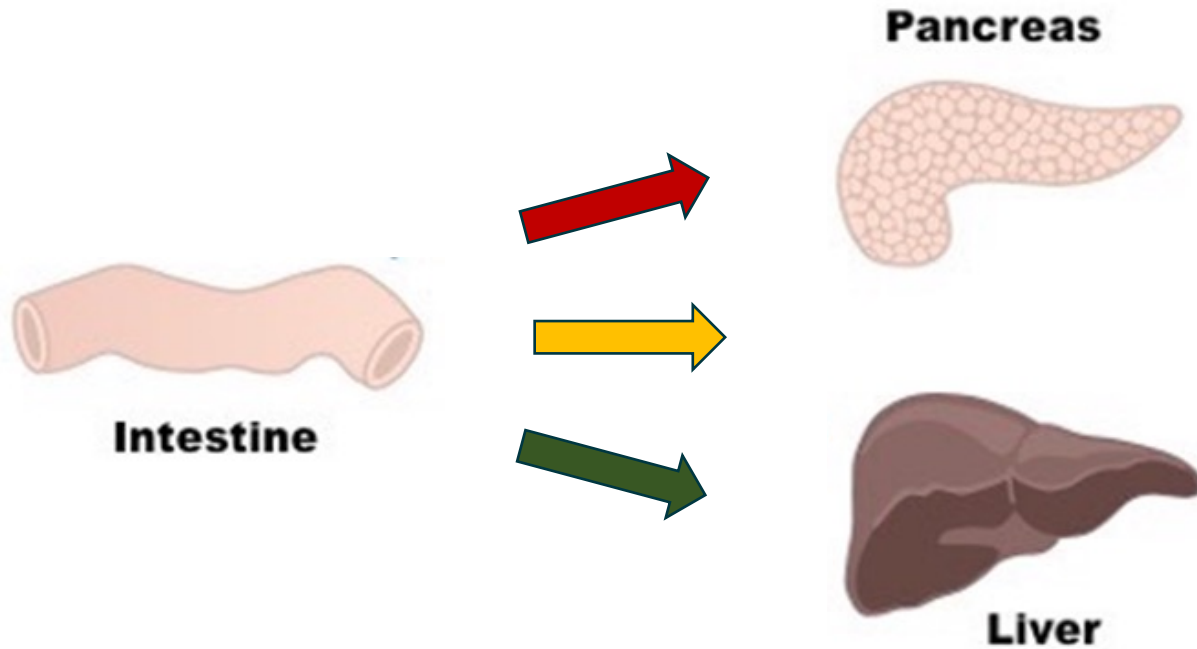
1. Post-prandial incretin response

- Mixed meal test at baseline vs. 6 mo.

2. Post-prandial bile acids response

- Mixed meal test at baseline vs. 6 mo

How did we investigate this?



1. Post-prandial incretin response

- Mixed meal test at baseline vs. 6 mo.

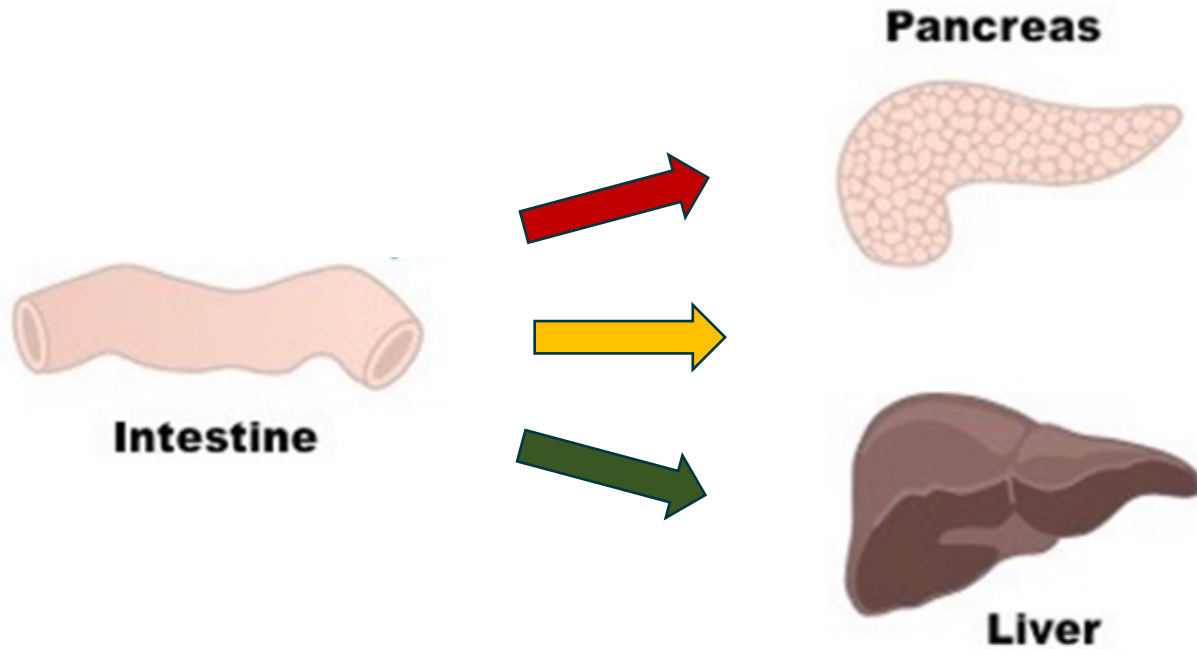
2. Post-prandial bile acids response

- Mixed meal test at baseline vs. 6 mo

3. Fecal microbiome diversity

- Fecal sample at baseline vs. 3 mo

How did we investigate this?



1. Post-prandial incretin response

- Mixed meal test at baseline vs. 6 mo.
- Incretin producing cells in biopsies

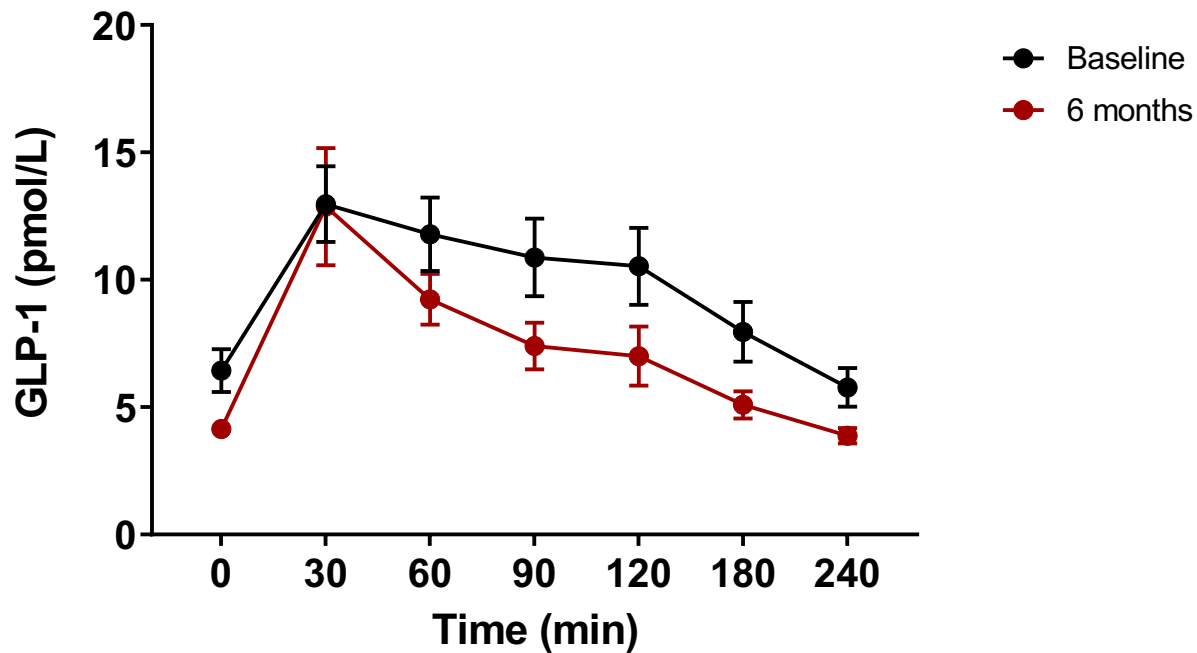
2. Post-prandial bile acids response

- Mixed meal test at baseline vs. 6 mo

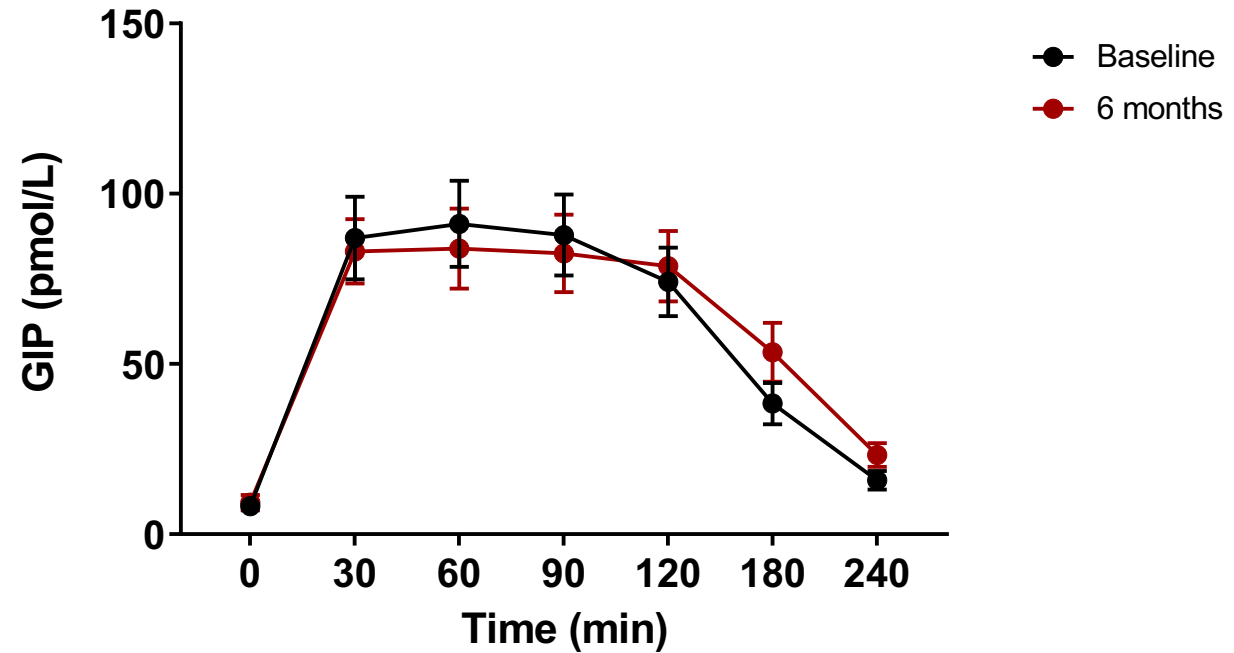
3. Fecal microbiome diversity

- Fecal sample at baseline vs. 3 mo

1. Incretins: GLP-1 + GIP



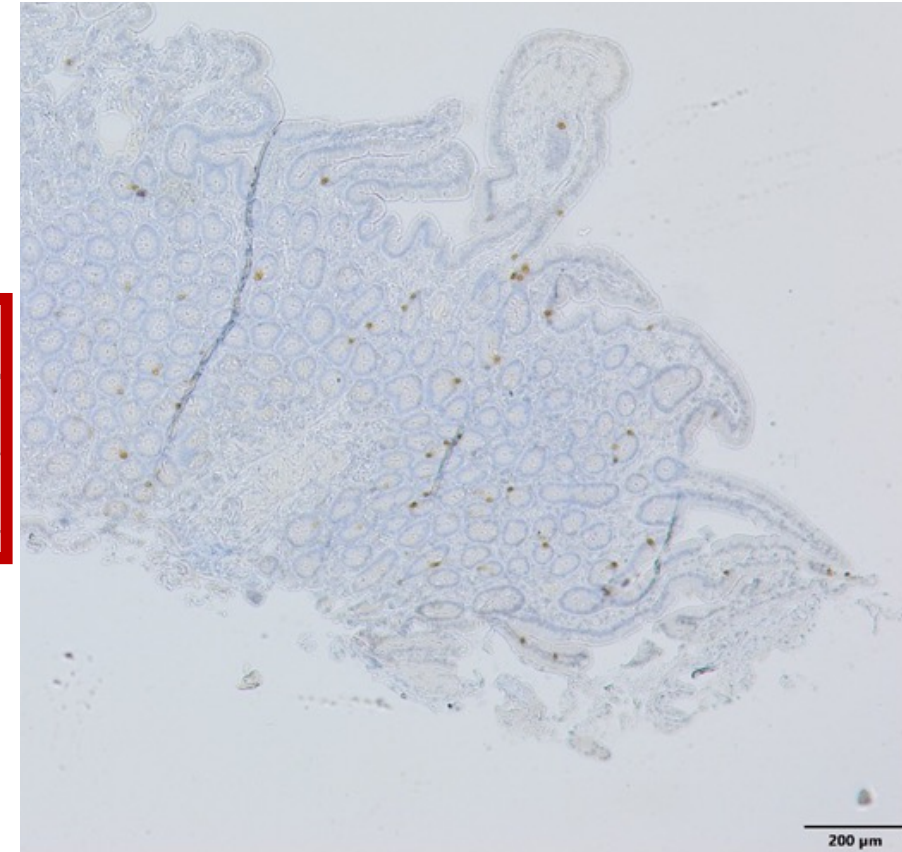
$p < 0.001$



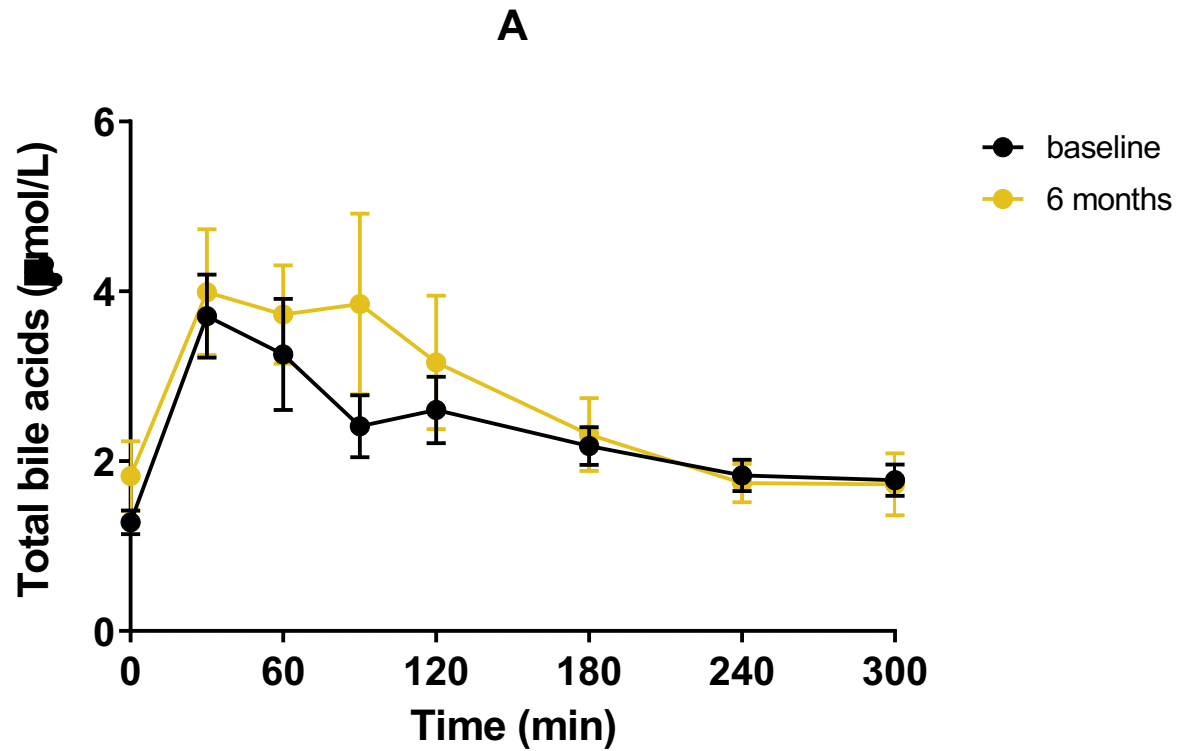
$p = 0.735$

1. Incretin-producing K and L cells

	Baseline	3 months	p-value
L-cell density [cells/mm ²]	6.37 (2.49-10.52)	5.47 (3.29-11.59)	0.28
K-cell density [cells/mm ²]	15.08 (6.54-24.46)	17.37 (14.79-22.82)	0.69



2. Postprandial bile acids response

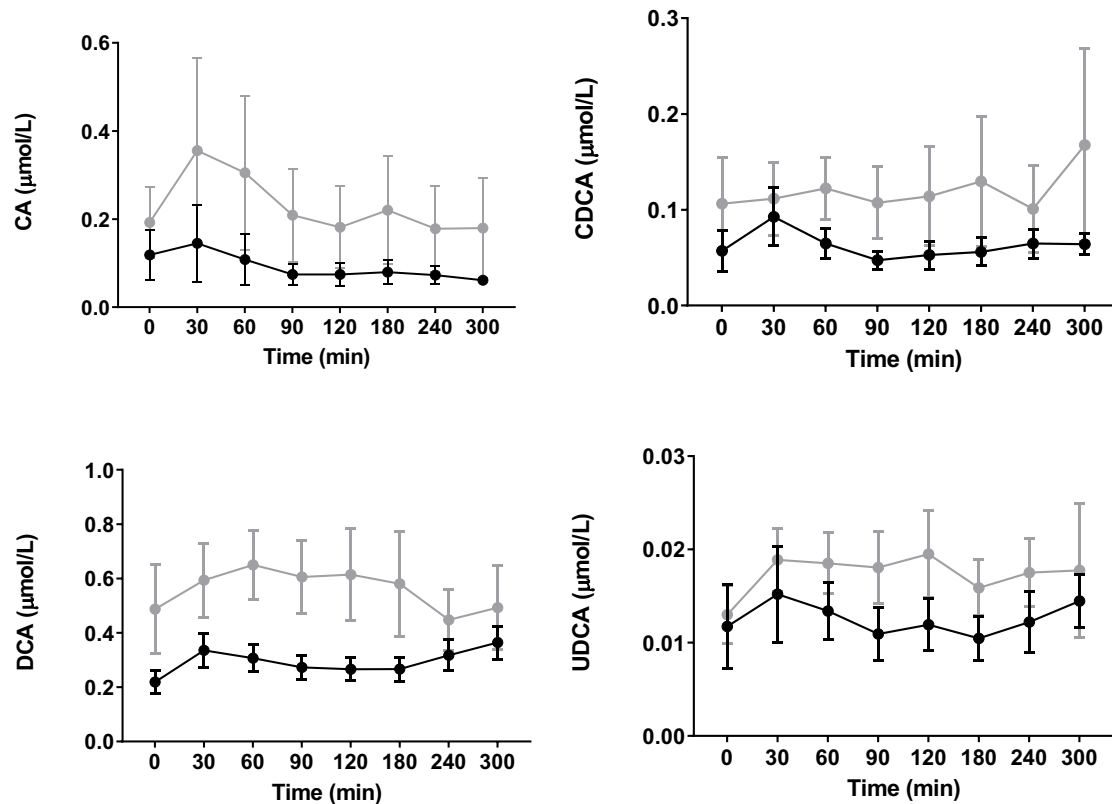


$p=0.124$

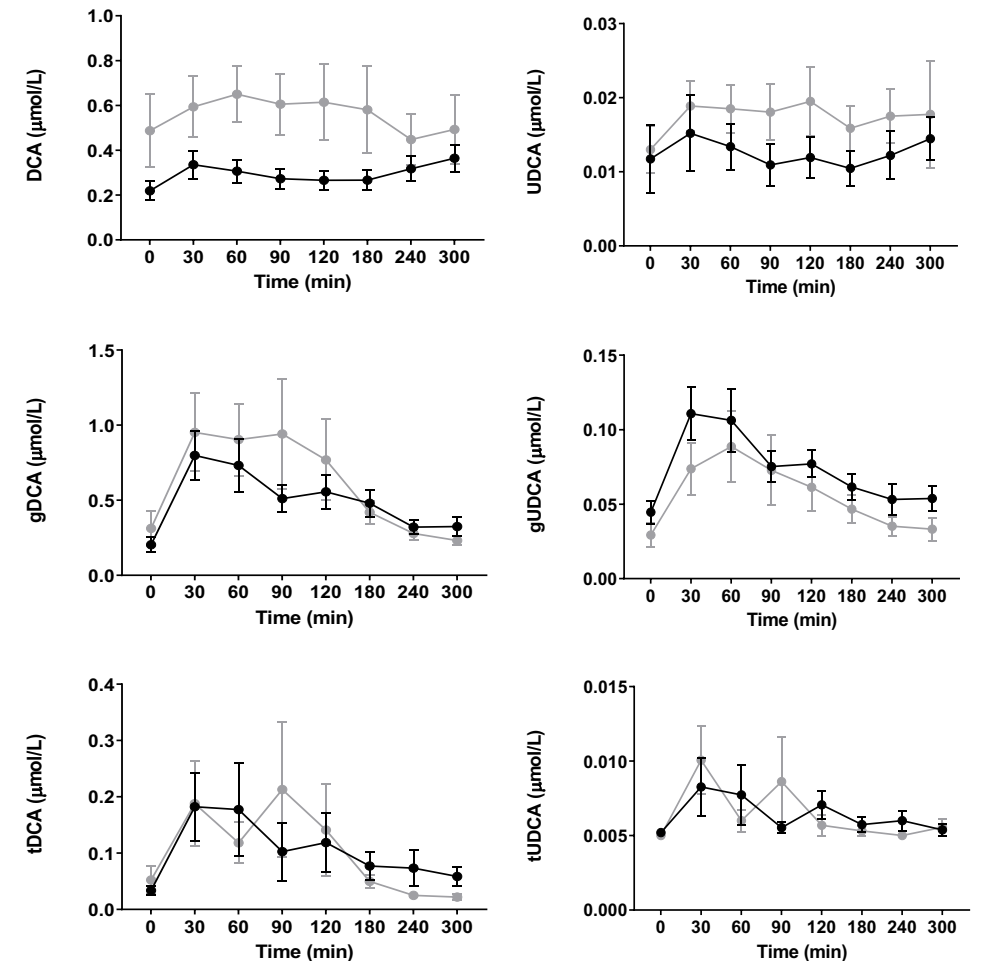
2. Postprandial bile acids response

● Baseline
● 6 months

Unconjugated BA increased:



Secondary BA increased:

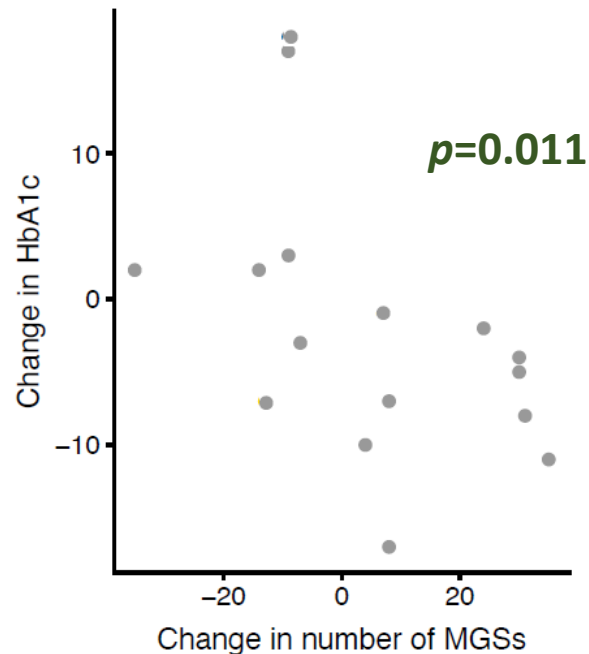


3. Fecal microbiome diversity

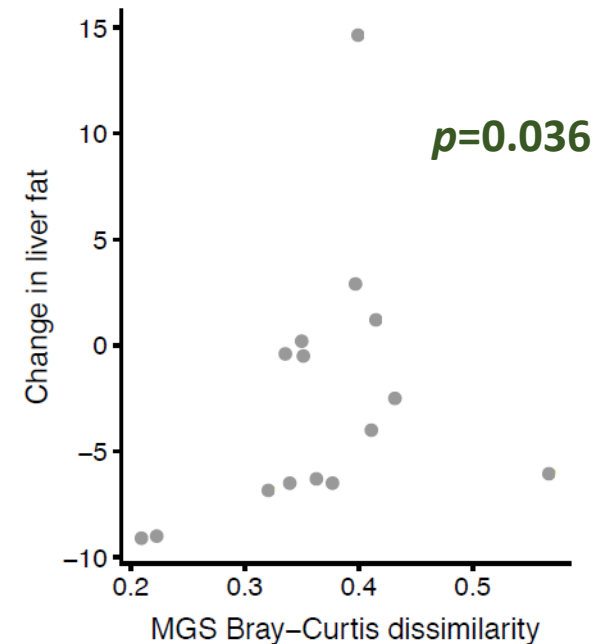
- Negative correlation between **HbA1c** and **microbiome diversity**

- **Change in liver fat** was correlated to **change in microbiome diversity**

Decreased HbA1c ~ Higher diversity



Changes liver fat ~ Changes diversity



Conclusions

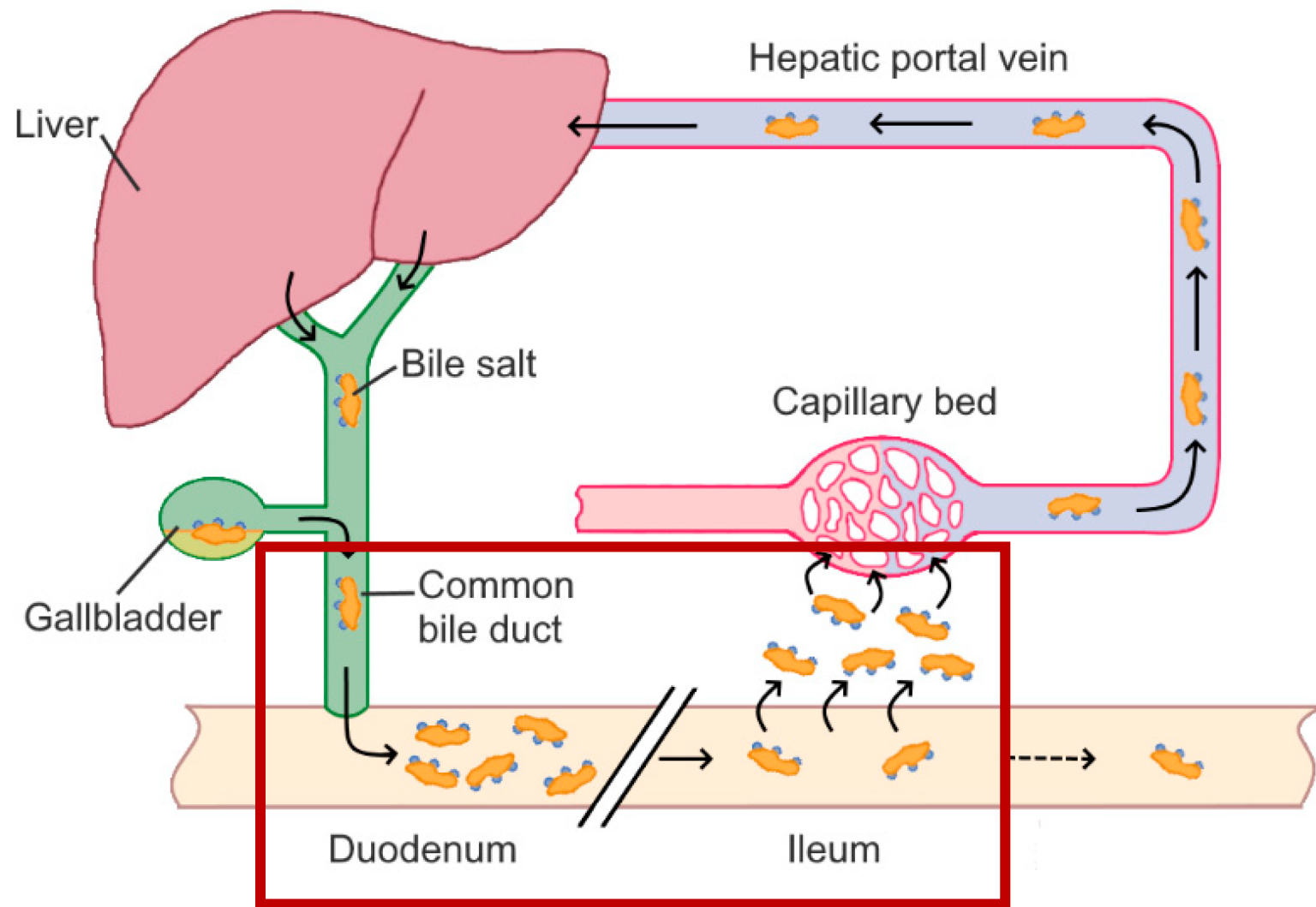
DMR + GLP-1RA results in improved metabolic health in T2D and comes with:

1. Decreased GLP-1 and unchanged GIP, unchanged L and K cell density
2. Increased unconjugated and secondary bile acids
3. Negative correlation between microbiome diversity and HbA1c

Discussion

DMR + GLP-1RA results in improved metabolic health in T2D and comes with:

1. Decreased GLP-1 and unchanged GIP, unchanged L and K cell density
 - Might reflect a negative feedback after exogenous GLP-1RA administration
2. Increased unconjugated and secondary bile acids
 - Might reflect the changes in the gut microbiome



Discussion

DMR + GLP-1RA results in improved metabolic health in T2D and comes with:

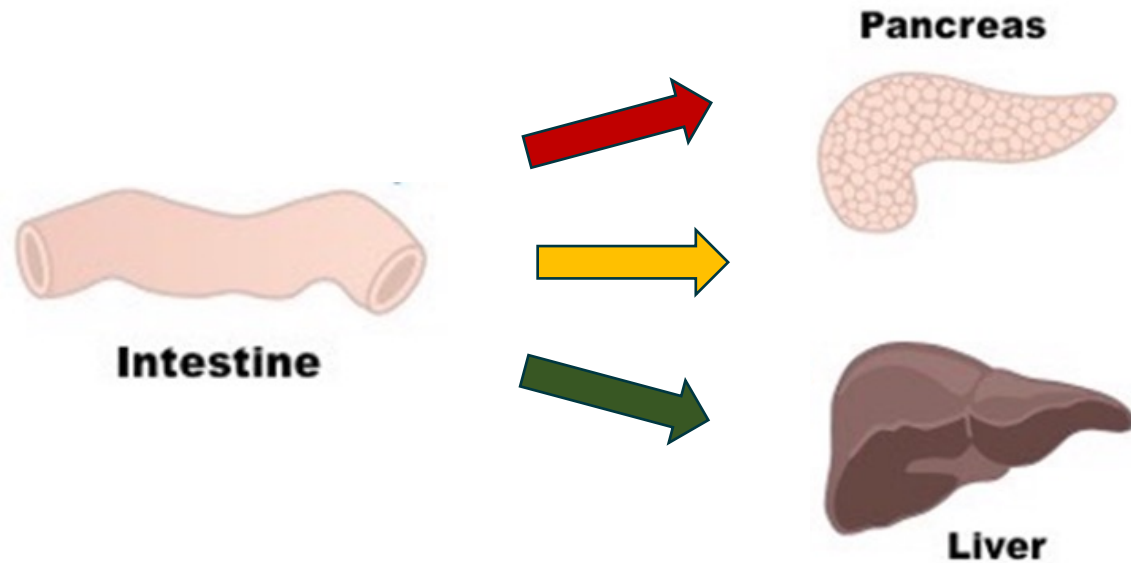
1. Decreased GLP-1 and unchanged GIP, unchanged L and K cell density
 - Might reflect a negative feedback after exogenous GLP-1RA administration
2. Increased unconjugated and secondary bile acids
 - Might reflect the changes in the gut microbiome
3. Negative correlation between microbiome diversity and HbA1c
 - In line with findings after bariatric surgery and Endobarrier

Limitations

- Small sample size
- Uncontrolled study:
Effect of DMR and GLP-1RA can not be separated.

Future:

- Larger controlled trials, investigating:



1. Incretins: GLP-1 + GIP

- Without exogenous GLP-1

2. Bile Acids

- Post-prandial and fecal

3. Microbiome

Questions ?