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Fecal microbiota trasplant using endoscopic-placement hydrogel reduces liver fibrosis with no changes in steatosis in a rat model of steatohepatitis with fibrosis

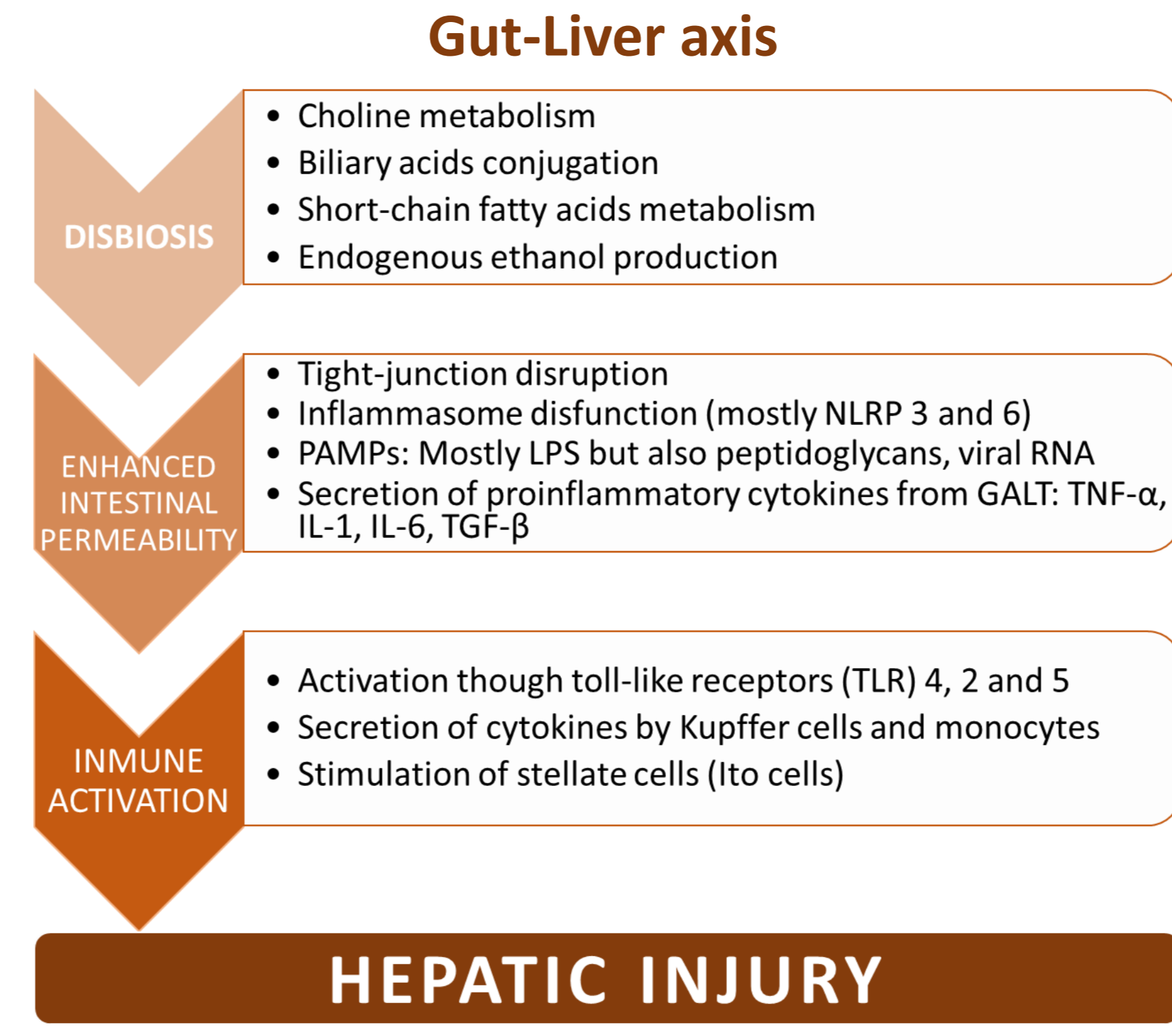


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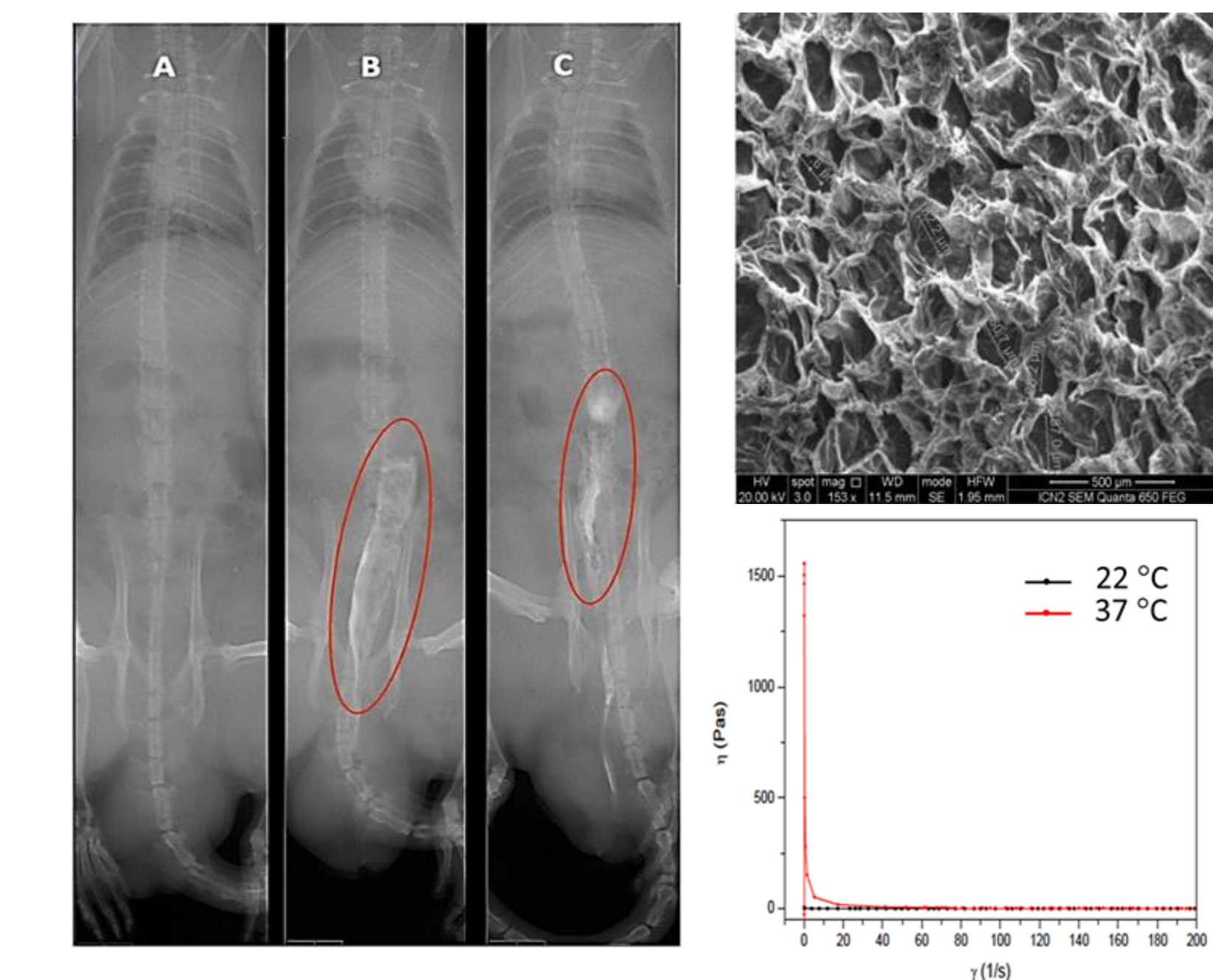
1 Introduction

The intestinal microbiota (IM) has emerged as a key factor in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) in addition to genetic predisposition, environmental factors and insulin resistance. This has led to propose the restoration of healthy intestinal microbiota (IM) with fecal microbiota transplantation (FMT) as a promising therapeutic strategy in the treatment of this disease. However, effective colonization of the colon is difficult to achieve. Our group has developed a hydrogel for endoscopic placement (Covergel) capable of releasing substances, which, used as a vehicle, could improve the effectiveness of FMT



Endoscopic placement hydrogel Covergel®

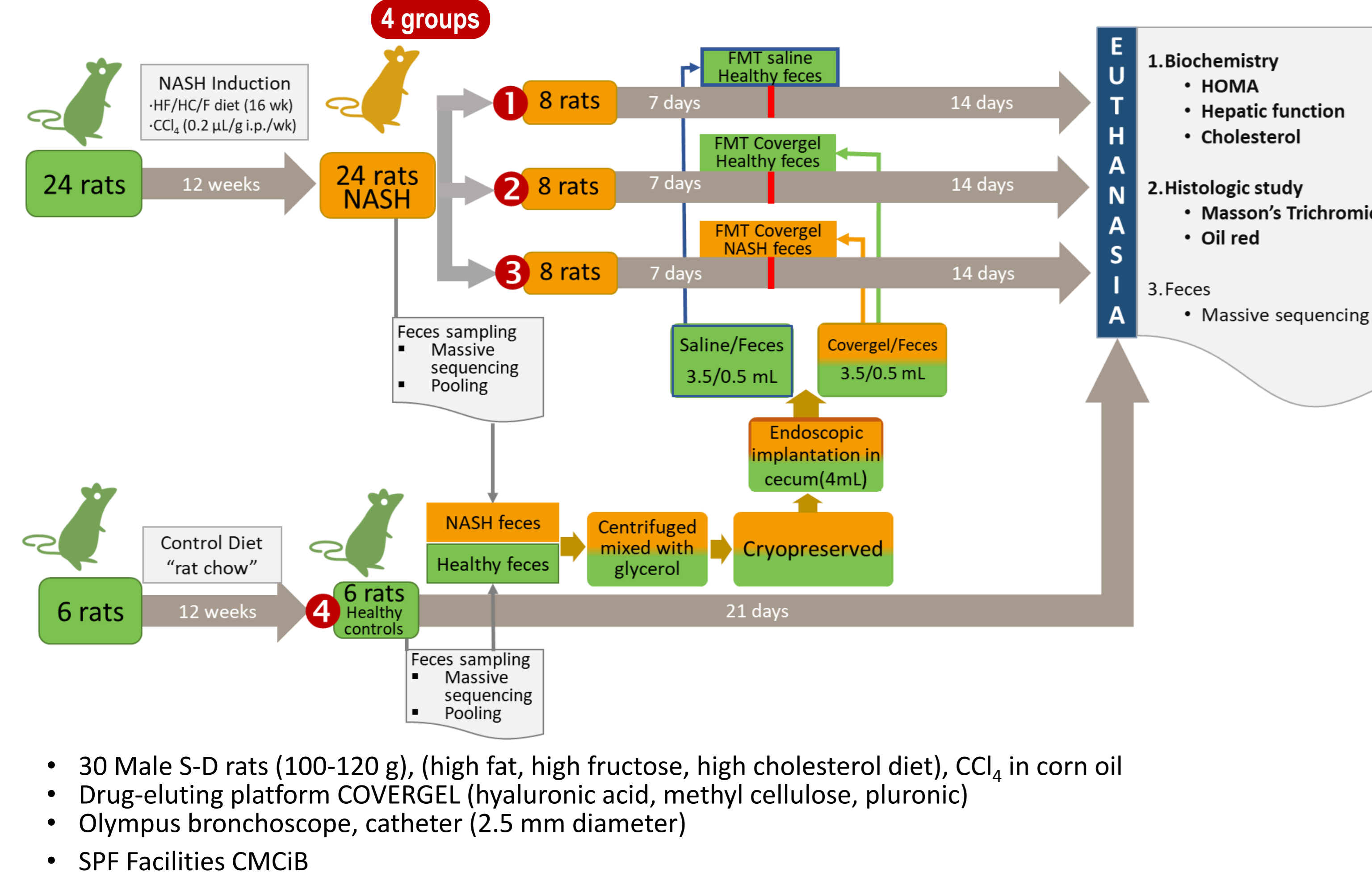
A reverse thermal gelation composition developed by our group (liquid at room temperature and solid at 37°C)



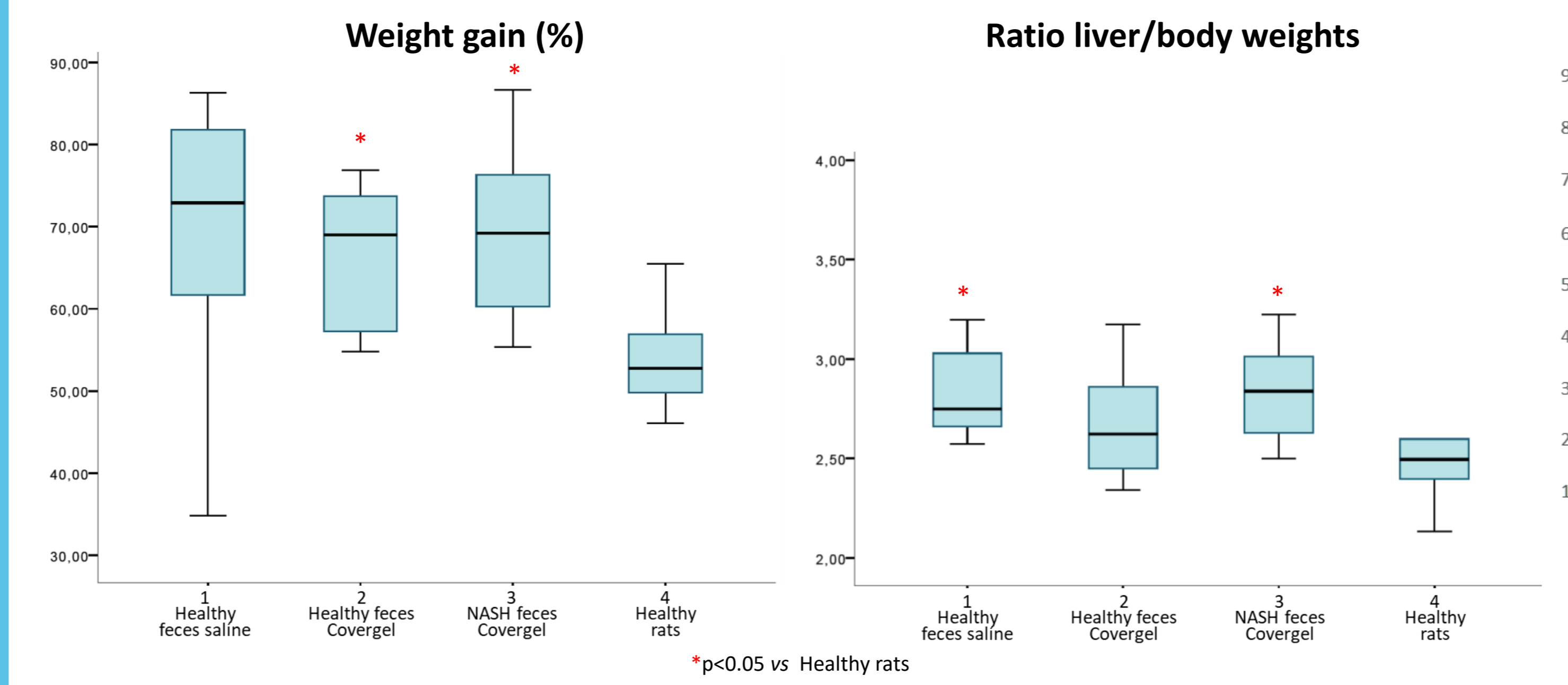
2 Hypothesis and Aim

IM restoration using FMT would have a beneficial effect on liver damage, being a useful therapeutic strategy in NAFLD. The use of the Covergel platform would increase the effectiveness of TMF by improving the colonization of the transplanted microbiota. In an animal model of steatohepatitis with fibrosis we aimed to assess:
 > The role of the intestinal microbiota in the mechanisms leading to steatosis and fibrosis.
 > The effectiveness of Covergel for the delivery of FMT with single colonoscopy vs the standard method

3 Method



4 Results



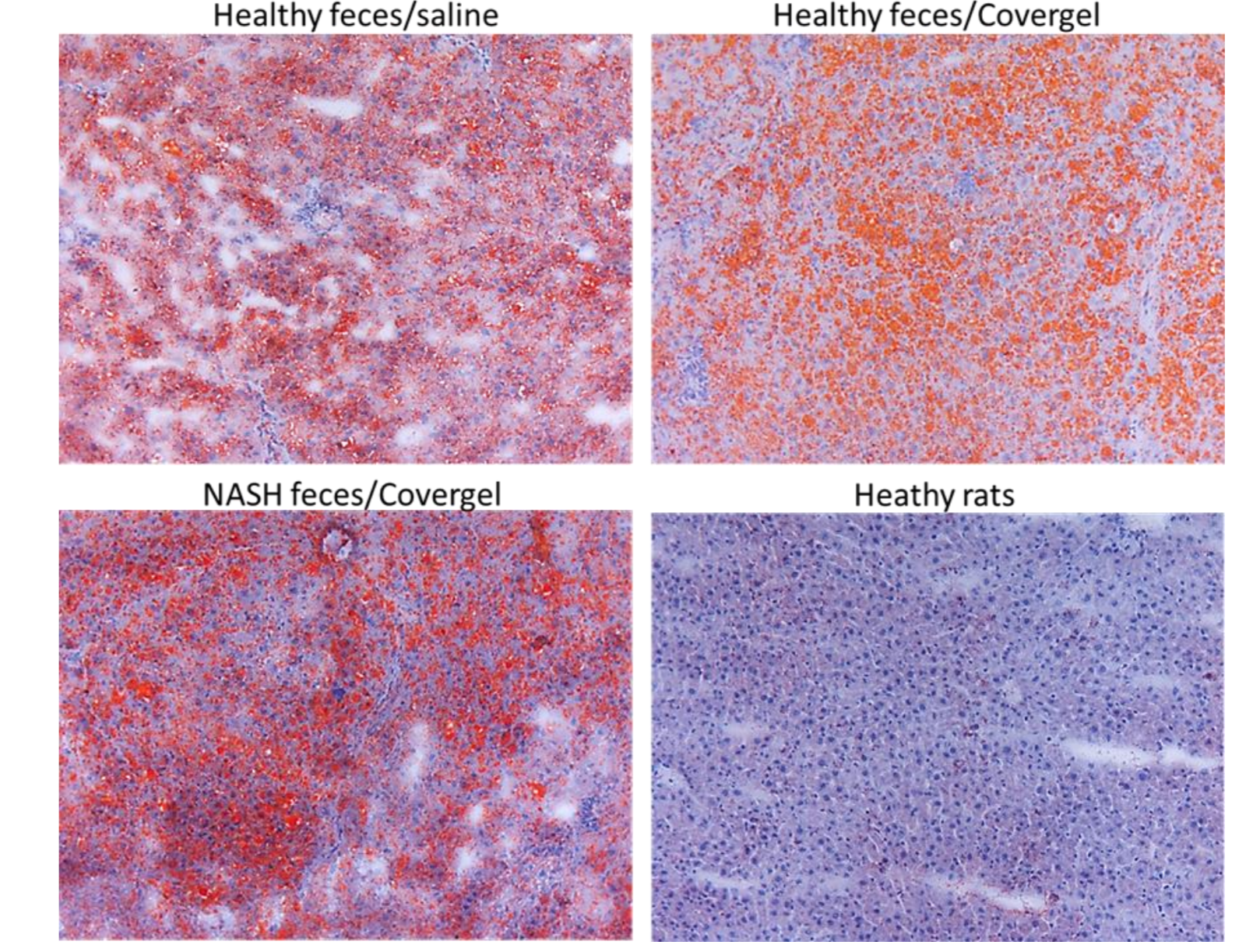
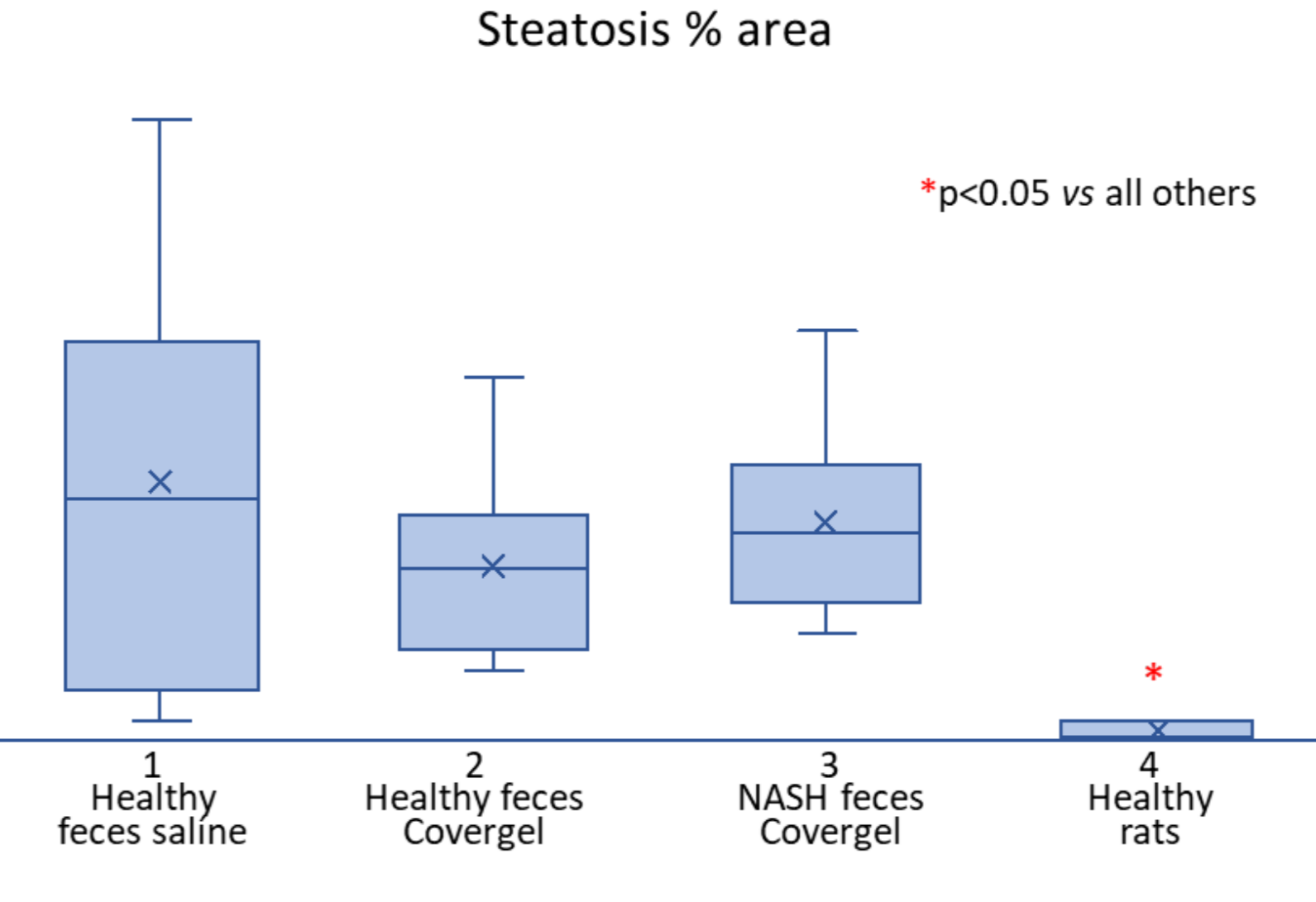
All animals with NASH and fibrosis show an increase in total weight and in the liver/body weight ratio. Although the different FMT procedures do not show significant differences in total weight, a normalization in the liver/body weight ratio is achieved in the FMT-Covergel group (2 vs 4, p=0.110).

Plasma biochemistry

GROUP	Albumin mg/dL	Bilirubin mg/dL	Alkaline Ph. U/L	AST U/L	ALT U/L	HDL mg/dL	LDL mg/dL	Triglycerides mg/dl	HOMA IR
Healthy feces saline	31,8 \pm 1,7	0,16 \pm 0,4	305,0 \pm 83,9*	102,7 \pm 39,5	56,63 \pm 7,2*	42,1 \pm 7,7*	16,4 \pm 7,3*	63,2 \pm 19,2	4,44 \pm 3,6
Healthy feces covergel	30,6 \pm 1,3	0,15 \pm 0,5	157,0 \pm 30,9#	96,4 \pm 52,6	46,5 \pm 12,9*	35,7 \pm 5,7*	22,3 \pm 8,7	73,7 \pm 13,5	5,45 \pm 3,3
NASH feces covergel	30,4 \pm 1,3	0,15 \pm 0,4	265,1 \pm 51,6*	87,5 \pm 31,7	42,6 \pm 5,8*	40,9 \pm 3,8*	19,1 \pm 4,6*	83,4 \pm 12,2	11,08 \pm 23,2
Healthy rats	31,7 \pm 1,6	0,17 \pm 0,3	88,0 \pm 11,5	72,8 \pm 15,1	30,2 \pm 3,4	58,1 \pm 5,3	24,3 \pm 4,2	78,7 \pm 12,0	3,67 \pm 3,5

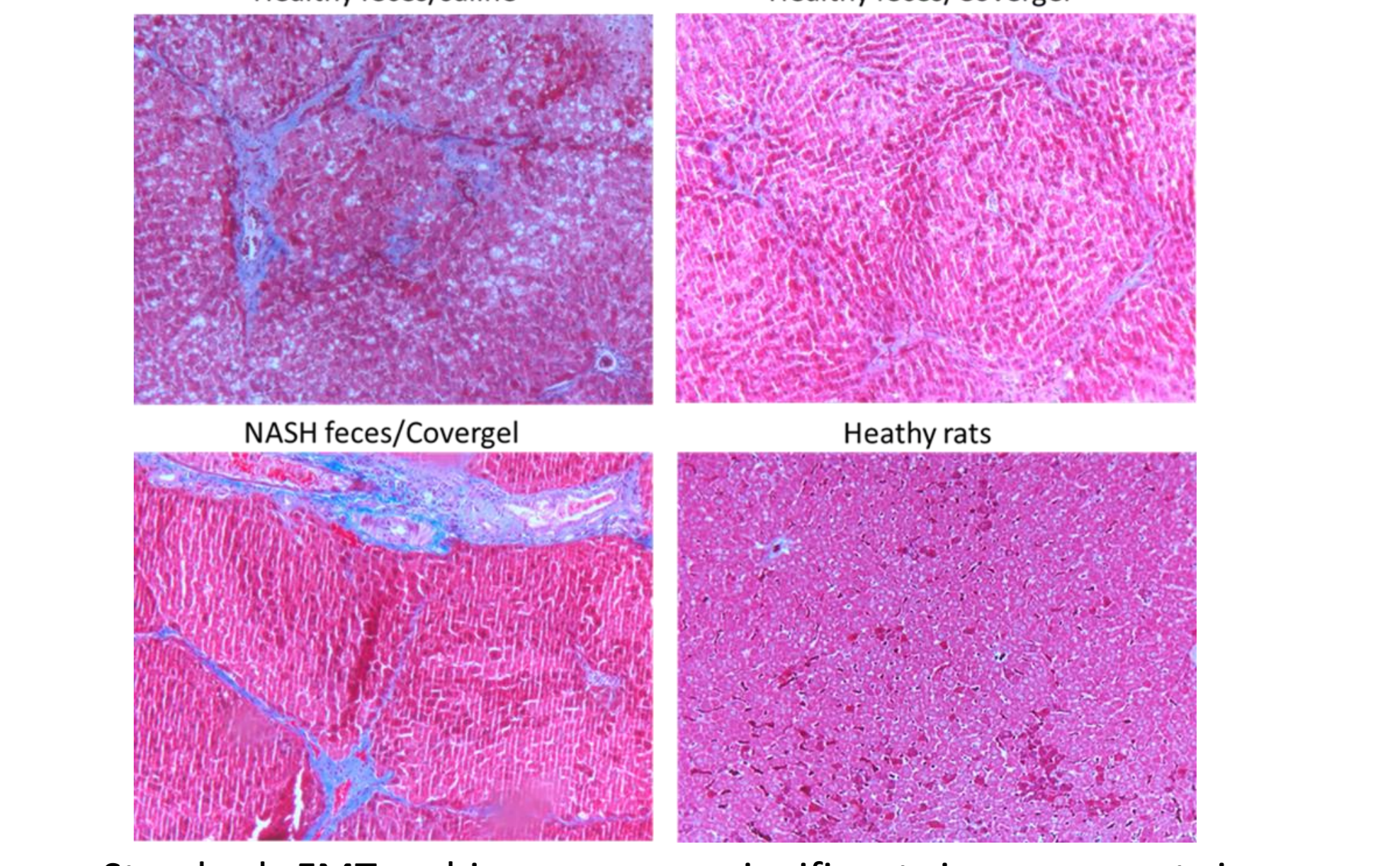
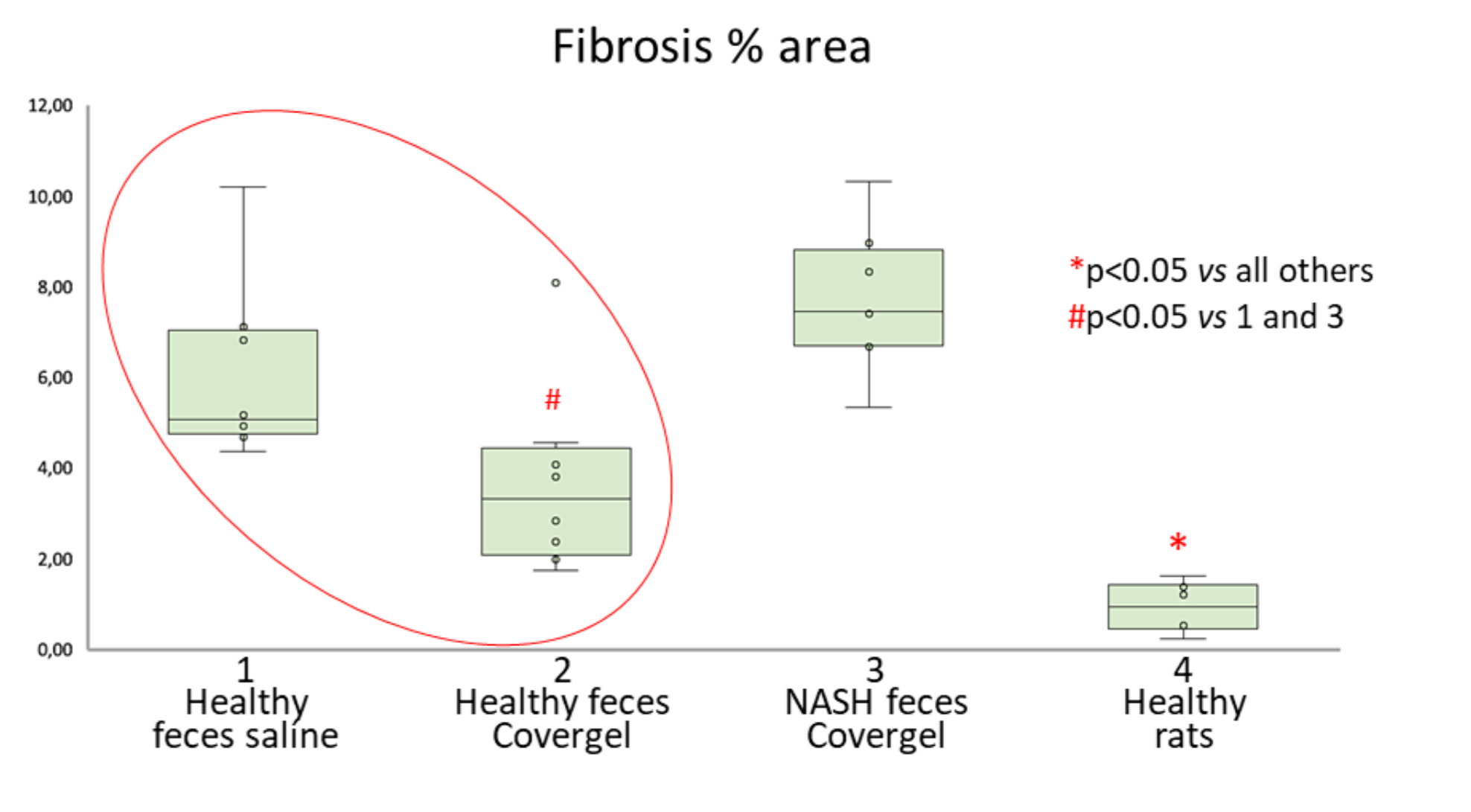
*p<0,05 vs group 4, #p<0,05 vs groups 1 and 3

Hepatic histologic analysis: steatosis degree (Oil red)



The TMF do not promote significant changes in steatosis degree.

Hepatic histologic analysis: fibrosis degree (Mason's Trichromic)



Standard FMT achieves a non-significant improvement in hepatic fibrosis (1 vs 3, p=0.084). In contrast, TMF-Covergel shows a significant improvement in it (2 vs 3, p=0.001). In addition, the reduction in fibrosis is significantly higher with TMF-Covergel compared to standard TMF (2 vs 1, p=0.034).

5 Conclusions

- Fecal microbiota transplantation using Covergel significantly reduces liver to weight ratio, normalizes phosphatase alkaline and LDL-cholesterol and significantly reduces fibrosis without significant attenuation of the ongoing steatosis.
- The use of Covergel would be an advantage, since the prolonged residence time of the hydrogel adhered to the mucosa would facilitate microorganisms colonization with a single colonoscopy.

6 References

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