Probiotic intervention to reduce postoperative inflammation in liver transplantation

Guenther Koellinger[1], Michael Treiber[1,] Florian Prueller[2], Rene Pilz[3], Philipp Stiegler[1], Robert Sucher[1], Peter Schemmer*[4], Judith Kahn[1]

1General, Visceral and Transplant Surgery, Department of Surgery, University Hospital, Medical University of Graz, Graz, Austria; 2Clinical Institute of Medical and Chemical Laboratory Diagnostics, University Hospital, Medical University of Graz, Graz, Austria; 3Department of Psychiatry, Psychosomatics and Psychotherapeutic Medicine , University Hospital, Medical University of Graz, Graz, Austria; 4Bern Visceral Surgery & Pancreas Clinic Switzerland, Hirslanden Hospital Beau-Site, Bern, Switzerland. *Initial PI of the study

Background

End-stage liver failure as an indication for liver transplantation (LT) and the associated changes in the microbiome can lead to the entry of potentially pathogenic pathogens and their metabolites from the intestine into the bloodstream and thus to pathologically increased inflammation, which can be critical in the context of major surgical procedures such as LT. Associated postoperative infections lead to increased morbidity and mortality, which are also associated with high treatment costs. Prophylactic perioperative pro- and synbiotics are intended to influence the postoperative inflammatory reactions in LT patients.

A meta-analysis of studies on the administration of pro-/synbiotics in LT [1] showed a reduction in postoperative clinical infections with a treatment duration of >10 weeks preoperatively to 14 days postoperatively with a pooled relative risk of 0.24, 95% CI: 0.12– 0.24, and improved postoperative liver function in one of 3 studies.

Patients and Methods

We performed a randomized, controlled, clinical pilot study including cirrhotic patients listed for LT. 5 patients were randomized in the intervention group with multispecies probiotic for at least 2 months before LT, 5 patients in the control group without probiotic therapy. Endotoxin concentration and inflammatory markers in peripheral and portal venous blood were measured pre-, peri- and postoperatively, as well as parameters of the intestinal barrier and liver function, clinical outcome, and additional assessment of QoL was performed.

This work was supported by AllergoSan (pharmazeutische Produkte Forschungs- und Vertriebs GmbH, Gmeinstraße 13, A-8055 Graz) (project-related support).

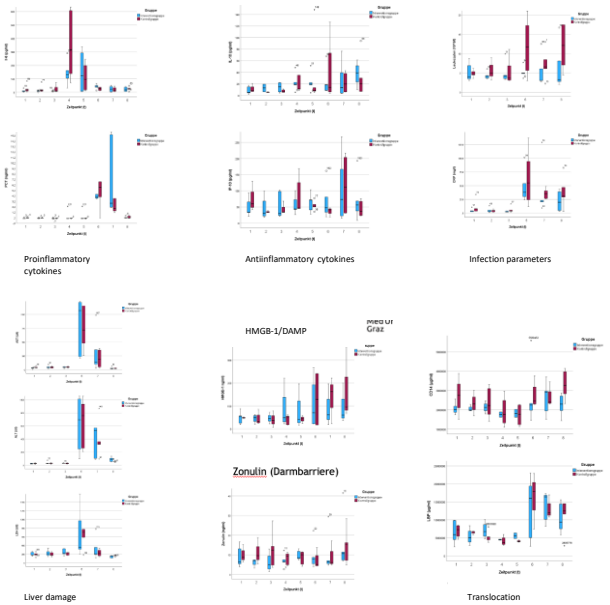


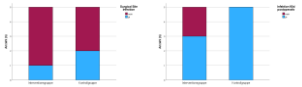
Fig. 1: Results: Inflammation, translocation, liver damage

Table 1: Patient characteristics

	Interventionsgruppe (n=5)	Kontrollgruppe (n=5)
Geschlecht		
männlich	4 (80%)	5 (100%)
weiblich	1 (20%)	0 (0%)
Alter zum Zeitpunkt der LTX (y)	60 (57-68)	61 (49-70)
Grunderkrankung		
Alcoholic liver disease (ALD)	3 (60%)	4 (80%)
Viral (HCV)	2 (40%)	1 (20%)
MELD	14 (6-18)	18 (8-20)
CHILD	7 (5-8)	6 (5-6)
MELD 2 Monate	13 (11-22)	15 (9-22)
CHILD 2 Monate	7 (5-9)	6 (5-8)

Results

There was no significant difference regarding intestinal translocation based on the measured surrogate parameters cluster of differentiation 14 (CD14) and lipopolysaccharide-binding protein (LBP), as well as the inflammatory and liver function parameters after LT and zonulin as a marker for intestinal barrier function between the two groups. Surgical site infection (SSI) rate was 20% in the intervention and 40% in the control group, duration of antimicrobial therapy after LT was 10 (0-109) days in the intervention group and 20 (0-39) days in the control group. Brief symptom inventory (BSI-18) showed significantly less somatization in the intervention group as compared with the controlgroup. .



- **Postoperative Infections:**

3-month infection rate 60% vs. 100%
SSI (month 1 post-LT) 20% vs. 40%

- **Hospital stay:**

21 (18-34) days intervention group vs. 21 (10-40) days control group

Fig. 2: Results: Clinical outcome

Conclusion

These results provide important insights for the planning of future clinical trials to investigate the influence of probiotic intervention on the outcome after LT.

1 Kahn J, Pregartner G, Schemmer P. Effects of both Pro- and Synbiotics in Liver Surgery and Transplantation with Special Focus on the Gut-Liver Axis-A Systematic Review and Meta-Analysis. Nutrients. 2020;12(8):2461.

Study design

- Prospective, monocentric, randomized pilot study

- Study population: Liver transplant (LT) candidates

  10 study participants/

  5 intervention group – 5 control group

- Study visits
  - Visit 1 Baseline/Listing for liver transplantation
  - Visit 2 Preoperative, 2 months from baseline
  - Visit 3 Directly preoperative
  - Visit 4 Perioperative
  - Visit 5 Perioperative
  - Visit 6 Postoperative day (POD) 1
  - Visit 7 POD 3
  - Visit 8 POD 10

Aim of the study

- Primary Endpoint

- Determination of the attenuation of endotoxmia measured over time in LT patients

- Secondary Endpoints

- Determination of the attenuation of the postoperative inflammatory response by perioperative measurement of cytokine levels
- Determination of gut barrier function
- Quality of life (QoL) assessment
- Clinical outcome

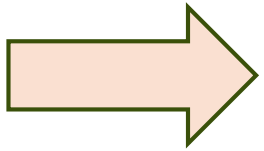
Patient characteristics

	Interventionsgruppe (n=5)	Kontrollgruppe (n=5)
Geschlecht		
männlich	4 (80%)	5 (100%)
weiblich	1 (20%)	0 (0%)
Alter zum Zeitpunkt der LTX (y)	60 (57-68)	61 (49-70)
Grunderkrankung		
Alcoholic liver disease (ALD)	3 (60%)	4 (80%)
Viral (HCV)	2 (40%)	1 (20%)
MELD	14 (6-18)	18 (8-20)
CHILD	7 (5-8)	6 (5-6)
MELD 2 Monate	13 (11-22)	15 (9-22)
CHILD 2 Monate	7 (5-9)	6 (5-8)

Study medication
OMNi-BiOTiC® HETOX

- OMNi-BiOTiC® HETOX
  - *Lactobacillus casei* W56
  - *Lactobacillus acidophilus* W37
  - *Lactobacillus brevis* W63
  - *Lactococcus lactis* W58
  - *Lactococcus lactis* W19
  - *Lactobacillus salivarius* W24
  - *Bifidobacterium lactis* W52
  - *Bifidobacterium lactis* W51
  - *Bifidobacterium bifidum* W23

  15 billion germs per portion (= 6 g)
- Duration of intake: minimum <u>2 months</u>



- Strengthening of the intestinal barrier/reducing intestinal permeability
- Inhibition of mast cell activation and proinflammatory cytokines
- Increase of the enzyme intestinal alkaline phosphatase: detoxification of lipopolysaccharides (LPS)

Results: Clinical outcome

- **Hospital stay:**

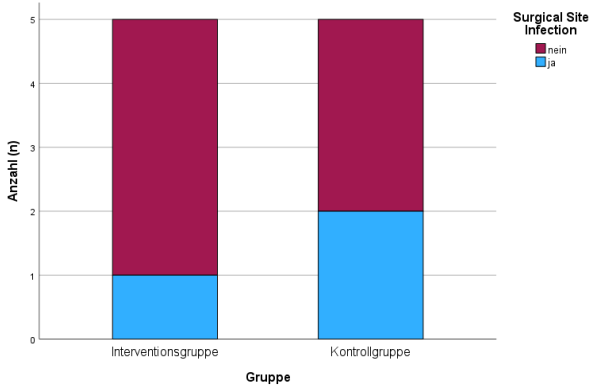
21 (18-34) days intervention group vs. 21 (10-40) days control group

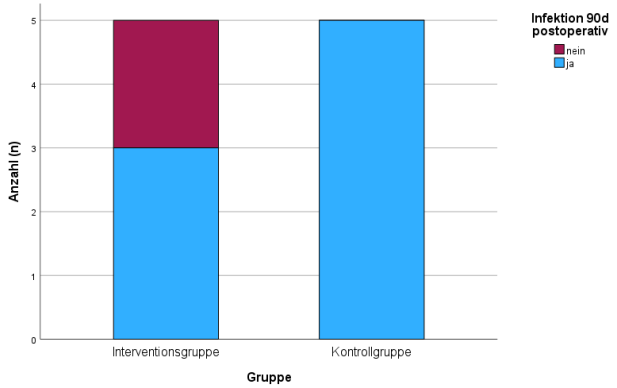
- **Duration of antiinfective therapy (3 months postOP):**

10 (0-109) days intervention group vs. 20 (0-39) days control group

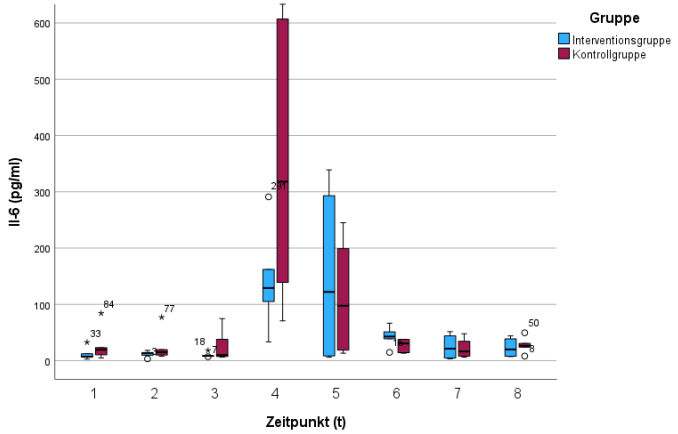
- **Postoperative infections:**

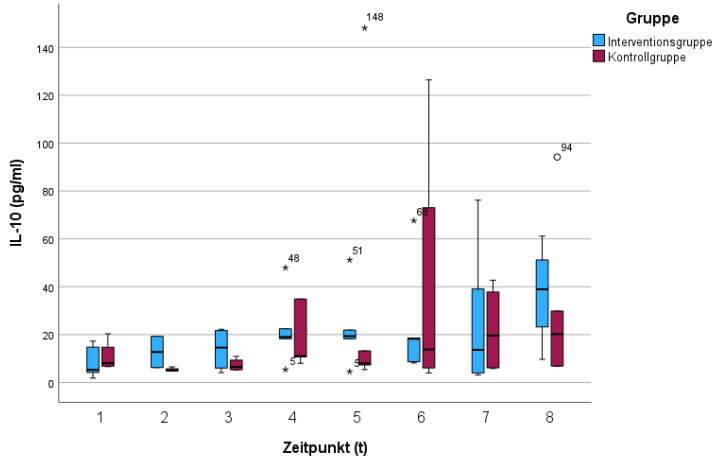
3-month infection rate 60% vs. 100%
SSI (month 1 post-LT) 20% vs. 40%

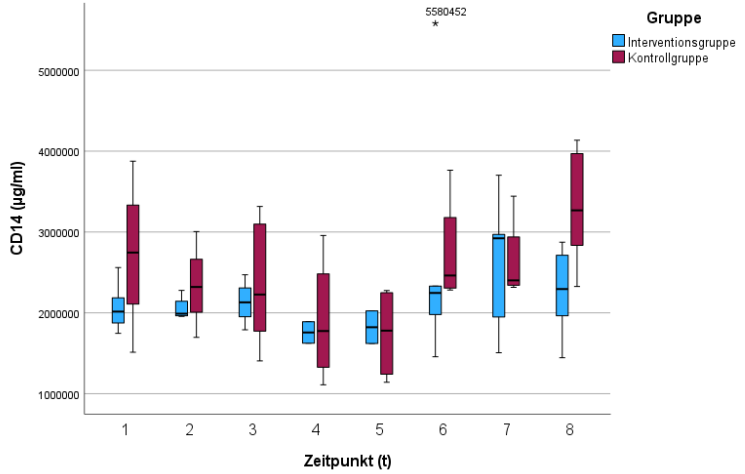


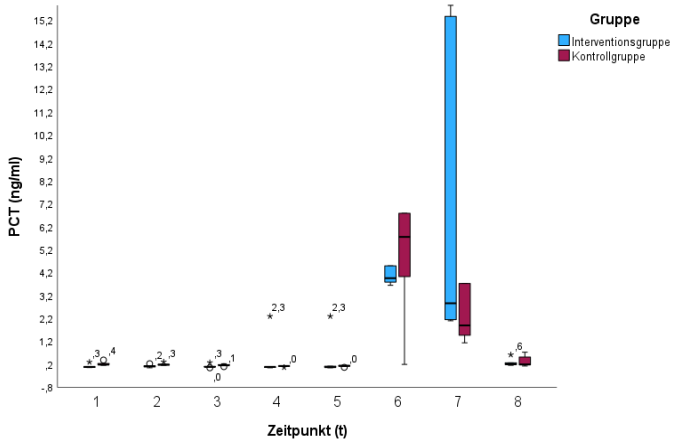


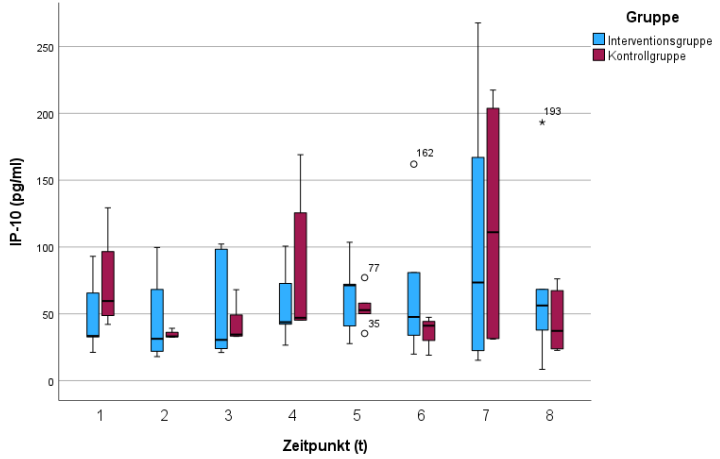
Results

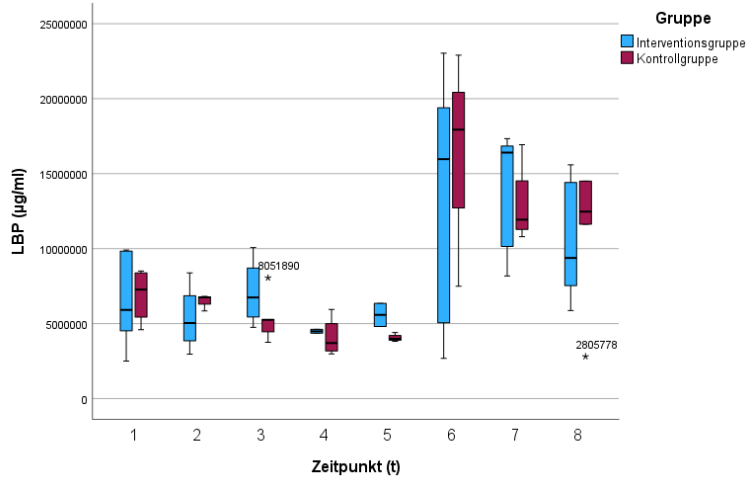










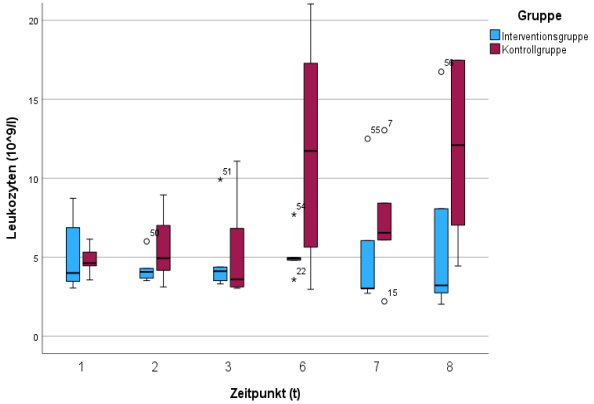


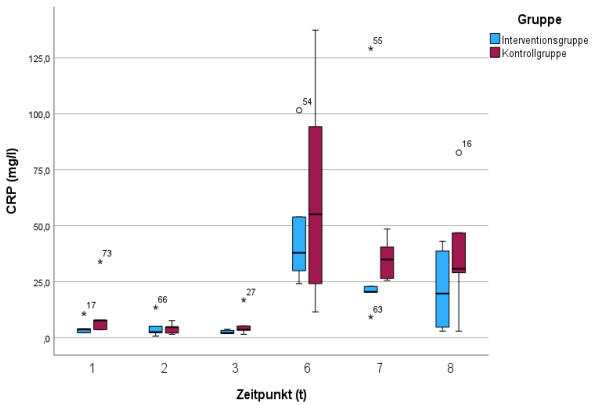
Proinflammatory cytokines

Antiinflammatory cytokines

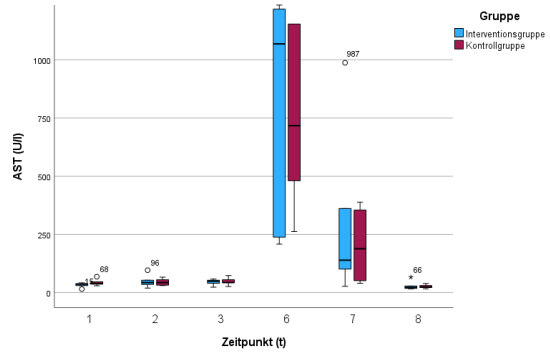
Translocation

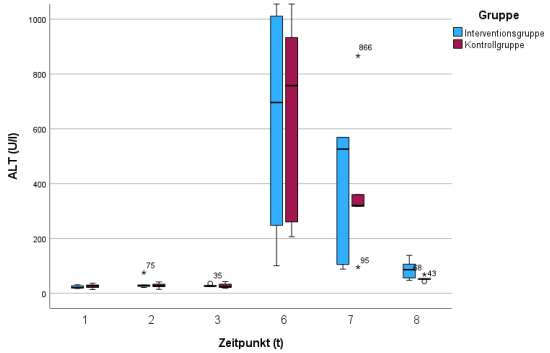
Results

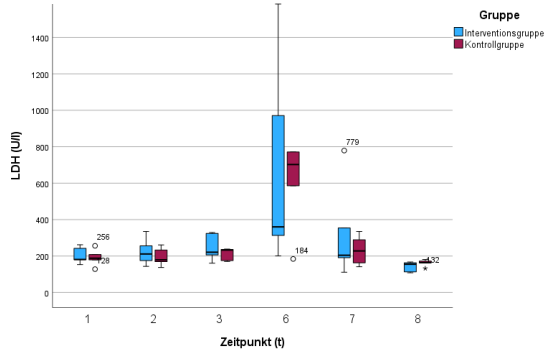




Inflammatory markers

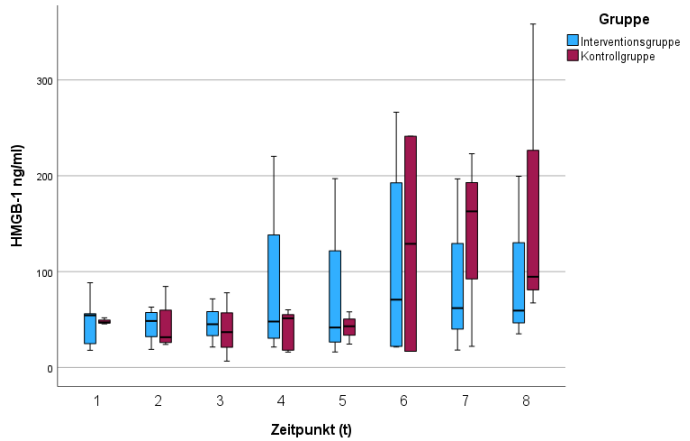




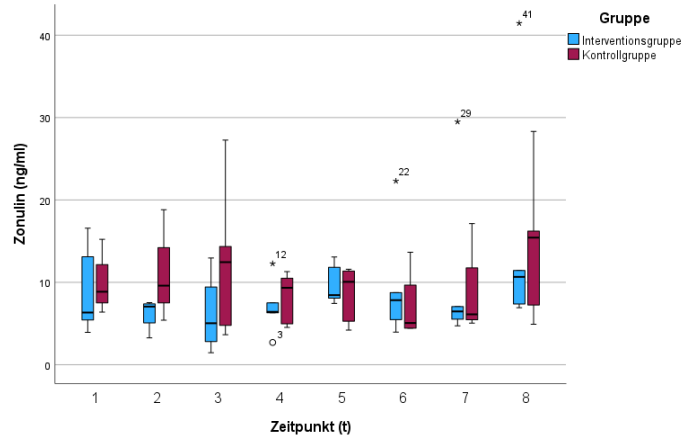


Liver damage

HMGB-1 / DAMP



Zonulin (intestinal barrier)



Results: Quality of life

SF-36:

- Physical health summary scale
- Psychical health summary scale
- Sum of health change
- and: Individual items

No difference

BSI-18:

- Anxiety
- Depression

No difference

- Somatization ↓ in Intervention group