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**ENDOTARGET/  
DEMONSTRATE IMPACT OF LOCAL AND SYSTEMIC LPS  
EFFECT ON JOINT DESTRUCTION IN IN VIVO OA ANIMAL**

WP3, Task 3.9

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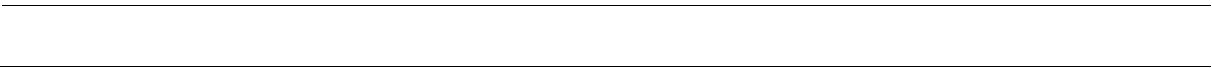
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## EXECUTIVE SUMMARY

This document reports experimental results from Task 3.9 for Deliverable 3.4 evaluating the influence of systemic and local lipopolysaccharide (LPS) exposure on the severity of arthritis in an in vivo rat model. Using male and female Wistar rats, LPS was administered either systemically or via intra-articular injection to assess how exposure route, dose and biological sex affect the immune activation and joint pathology.

Systemic inflammation was assessed by immunophenotyping of peripheral immune cells, while local inflammation was evaluated by immune cell infiltration within the synovial membrane and total synovitis score. Systemic LPS administration induced measurable peripheral innate immune activation with minimal synovial inflammation. In contrast, intra-articular LPS produced more pronounced immune cell infiltration in synovial membrane and overall higher synovitis score. Notably, sex-dependent immune responses were observed. Female animals showed higher sensitivity to systemic LPS and showed higher innate immune activation in response to chronic systemic LPS exposure, whereas male animals exhibited stronger local immune reaction triggered by intra-articular LPS.

Joint pathology was evaluated using histological grading of cartilage and quantitative microCT-based analysis of cartilage surface roughness. Overall, the results demonstrate that LPS modulates arthritic disease severity in a manner dependent on route of administration and biological sex. Systemic LPS induced mild cartilage matrix degradation and cartilage defects, with more severe changes in females than males. In contrast, intra-articular LPS induced moderately higher cartilage matrix degradation but fewer cartilage defects, independent of sex.

This deliverable therefore fulfills its objective by providing experimental evidence on the role of local and systemic LPS exposure in arthritis severity in a preclinical rat model.

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## LIST OF ABBREVIATIONS

| ACRONYM | DESCRIPTION                                 |
|---------|---------------------------------------------|
| OA      | Osteoarthritis                              |
| LPS     | Lipopolysaccharide                          |
| E. Coli | Escherichia coli                            |
| NaCl    | Sodium Chloride                             |
| K2EDTA  | dipotassium ethylenediaminetetraacetic acid |
| SF      | Synovial fluid                              |
| PFA     | Paraformaldehyde                            |
| EU      | Endotoxin Unit                              |
| microCT | Micro Computed Tomography                   |

|       |                                               |
|-------|-----------------------------------------------|
| CRS   | Cartilage roughness score                     |
| HE    | Hetatoxylin and Eosin                         |
| Saf-O | Safranin-O                                    |
| TB    | Toluidine blue and Fast green                 |
| OARSI | Osteoarthritis Research Society International |
| CDS   | Cartilage degeneration score                  |
| AE    | Adverse event                                 |
| CI    | Confidence interval                           |
| LFC   | Lateral femoral condyle                       |
| MFC   | Medial femoral condyle                        |
| LTP   | Lateral tibia plateau                         |
| MTP   | Medial tibia plateau                          |
| inj   | Injection                                     |
| d     | Day                                           |
| WP    | Work package                                  |

## 1. INTRODUCTION

This report presents the experimental work conducted under Task 3.9 and Deliverable 3.4 of ENDOTARGET project. We aim to assess the influence of LPS on the severity of arthritis in a rat model. This work evaluates how systemic and local LPS exposure affects inflammatory responses and joint pathology.

To address this objective, male and female Wistar rats were subjected to continuous systemic or intra-articular administration of LPS using consortium-identified reference LPS. The impact of LPS exposure was assessed through monitoring of systemic immune activation, evaluation of local immune cell infiltration and comprehensive joint-level analysis, including histological evaluation of cartilage

matrix degradation and quantitative microCT-based assessment of cartilage surface integrity. The results presented in this deliverable report provide experimental evidence distinguishing the effects of systemic and local LPS in modulating arthritis and directly contribute to the objectives of Work Package 3.

## 2. METHODOLOGY

### 2.1 TYPE OF LPS FOR THE ANIMAL TRIAL

Commercial E.Coli O26:B6 LPS was purchased from Merck (Cat. L2654) and used. This type of LPS is used as positive inflammatory control in WP2 and WP3. This product was prepared by gel-infiltration chromatography and sterilized using  $\gamma$ -irradiation. The batch of LPS used in this study has 3,000,000 endotoxin unit (EU) per microgram of product, and the impurity is 1.28% protein. The LPS was dissolved in sterile NaCl 0.9% (B.Braun, Cat. 29554) to 4mg/ml (w/v) and stored in  $-20^{\circ}\text{C}$  for further studies.

### 2.2 MODEL ESTABLISHMENT AND SAFETY SCREENING

To establish the continuous systemic delivery model and to optimise the LPS dose to be given to animals, we used osmotic pumps (Alzet, 2ML4) that could systemically and constantly deliver LPSs to the animals at a mean flow rate of  $2.38 \pm 0.08 \mu\text{l/hr}$  for 28 days. The pumps loaded with various concentration of LPSs were implanted subcutaneously at the back of the 6-month-old male and female Wistar rats to enable a delivery of 18 microgram per kilograms of body weight per day ( $\mu\text{g/kg/d}$ ) (low-LPS),  $75 \mu\text{g/kg/d}$  (mid-LPS) or  $300 \mu\text{g/kg/d}$  (high-LPS) of LPS solution for a period for 28 days. Healthy control animals (No LPS) received pumps loaded with sterile saline. 0.7ml peripheral blood was collected from the sublingual vein once every two weeks for LPS measurement and immune cell phenotyping. 10 weeks after the pump implantation, the animals were euthanised, knee synovial fluid (SF) and tissues were harvested for further analysis (Figure 1).

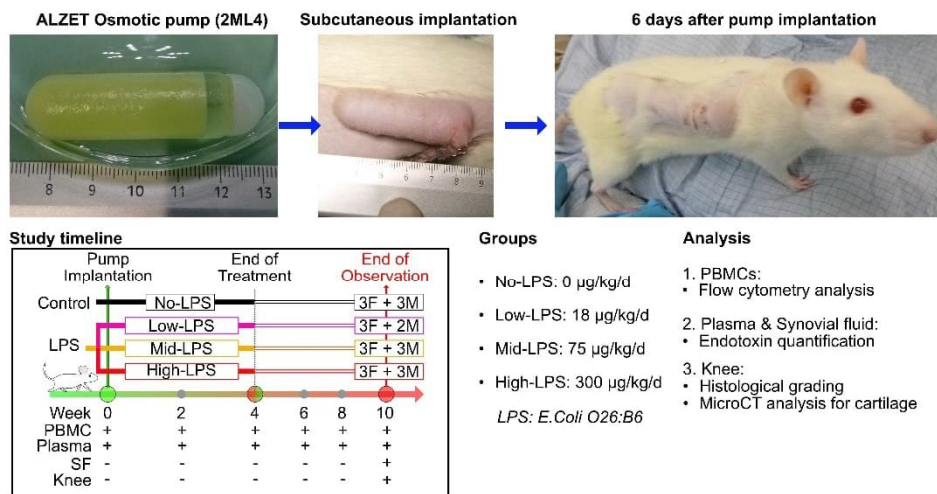


Figure 1. Study plan for dose-dependent animal trial

## 2.3 SYSTEMIC ADMINISTRATION OF LPS TO RATS

In this trial, an osmotic pump (Alzet, 2006) was used to systemically and constantly delivery LPS to the animals at a mean flow rate of  $0.15 \pm 0.01 \mu\text{l/hr}$ . The pumps were implanted subcutaneously at the back of the 6-month-old male and female Wistar rats to enable a delivery of  $18 \mu\text{g/kg/d}$  of LPS solution for a period for 42 days. Healthy control animals received pumps loaded with sterile 0.9% NaCl for 42 days. 10 weeks of post-implantation, the animals were euthanized, and peripheral blood was collected via cardiac puncture. Knee synovial fluid and knee tissues were collected for further analysis (Figure 2).

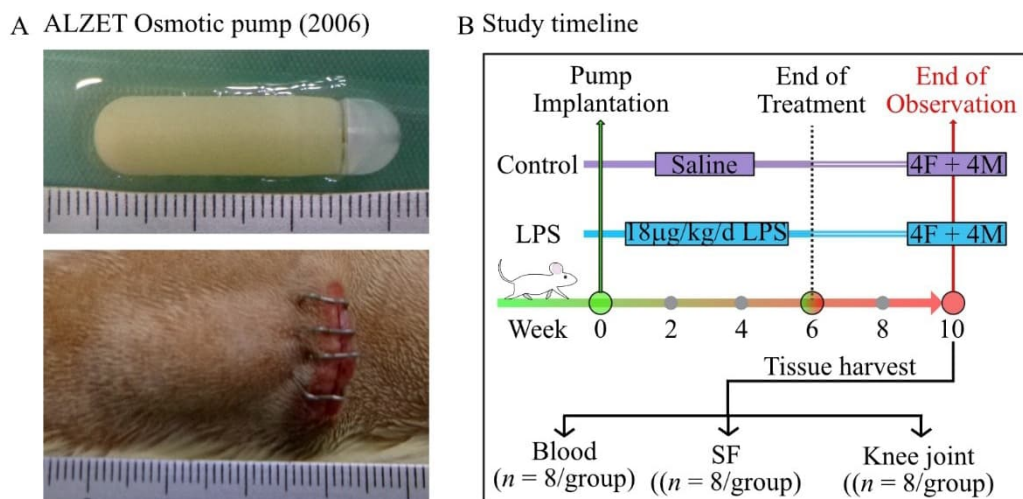


Figure 2. Study plan for time-dependent animal trial.

(A) (Top) Picture showing the size of the osmotic pump; (Bottom) The pump was placed subcutaneously at the back of the animal. (B) The study timeline.

## 2.4 INTRA-ARTICULAR ADMINISTRATION OF LPS TO RATS

6-month-old male and female rats were anesthetized by isoflurane inhalation and laid at supine position. The knee area was prepared and disinfected. 10µg LPS in 25µl 0.9% NaCl solution was injected using a 30G insulin syringe to the knee at day 0, day 2 and day 4. Control animals received 25µl of 0.9% NaCl solution injection. The animals were allowed to move freely after the procedure. And they are housed in standard housing conditions. 10 weeks of post-implantation, the animals were euthanized, and peripheral blood was collected via cardiac puncture. Knee synovial fluid and knee tissues were collected for further analysis (Figure 3).

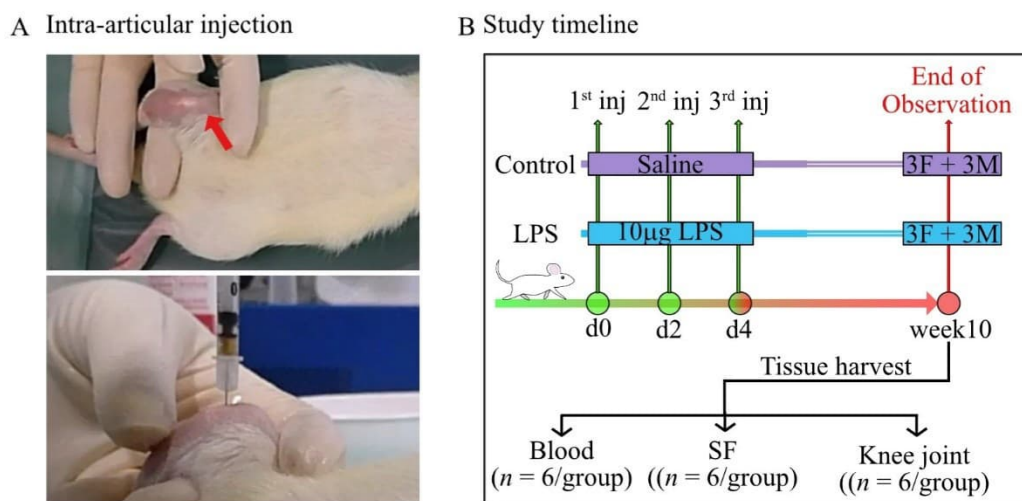


Figure 3. Study plan for intra-articular delivery of LPS animal trial.

(A) Demonstration of the intra-articular injection procedure. (Top) The animal was placed at supine position; the knee was flexed at 90° and the patellar tendon was located (red arrow). (Bottom) A 30G insulin needle was inserted at the middle of the patellar tendon into the knee joint cavity to inject the solution. (B) Study timeline. Three injections of either LPS or saline solution were injected to one knee. Inj: injection. d: day.

## 2.5 SAMPLE ANALYSIS

### 2.5.1 Immunophenotyping of peripheral immune cells

Rat's whole blood was collected into a K2EDTA blood collection tube (BD Vacutainer™) for peripheral immune cell isolation and subsequent characterization by flow cytometry. As previously described [1], immune cells were separated from whole blood after Ficoll-Paque density gradient centrifugation. The immune cells were then resuspended in buffer, stained with a panel of antibodies,

and characterized by flow cytometry. The percentage of monocytes and neutrophils were calculated.

### 2.5.2 Detection of LPS in blood plasma and synovial fluid

Plasma sample was phase-separated from the whole blood after Ficoll-Paque density gradient centrifugation. SF sample was aspirated from knee joint after animal euthanasia. LPS in plasma and SF was measured using Pierce™ Chromogenic Endotoxin Quant Kit (ThermoFisher Scientific, A39552) according to manufacturer's instructions.

### 2.5.3 Knee joint tissue analysis

After euthanasia, knee joints were harvested and immediately fixed in 4% paraformaldehyde (PFA) for 1 week. After fixation, the distal femur and tibia were dehydrated, 1% phosphotungstic acid (in 70% ethanol) for 24 h and scanned with a micro computed tomography (microCT) 45 device (Scanco Medical, CH). The scans were acquired at 55 kV, 72  $\mu$ A and 4W using an 0.5 mm aluminium filter (4.5  $\mu$ m voxel size). The cartilage roughness score (CRS) was calculated as described [1, 2]. The CRS represents the angular difference between the cartilage and reference surfaces averaged over the whole condyle. A high CRS therefore indicates increased surface roughness and cartilage damage.

The fixed joint synovial membrane, distal femurs and tibias were decalcified in aqueous 10% NH<sub>4</sub>-EDTA solution (joint capsule: 1 weeks, femur/tibia: 3 weeks), dehydrated, paraffinized on a Milestone Logos J device (Milestone, ITA) and embedded in paraffin blocks. Serial sections were cut at 5- $\mu$ m using a microtome. Hematoxylin and Eosin (HE). Safranin-O (Saf-O) and Toluidine blue/Fast green (TB) stainings were performed to assess the general morphology of the tissue as well as the glycosaminoglycan and proteoglycan content of the cartilage. Histopathological grading of synovium was performed using a synovium grading system proposed by *Krenn et al* [3]. Cartilage was evaluated using the cartilage degeneration score (CDS) described in the OARSI histopathology initiative [4].

### 3. RESULTS

#### 3.1 DOSE-RESPONSE OF ANIMAL TO SYSTEMIC ADMINISTRATION OF LPS

##### 3.1.1 The safety of systemic administration of LPS

We first monitored animals' behavior, appearance and body weight overtime to investigate the safety of LPS. In this trial, all females receiving the high dose of LPS developed skin ulcer around the pump after 6 weeks of implantation (Figure 4A). HE staining showed immune cell infiltration and fibrotic capsule formation in the subcutaneous layer (Figure 4B). Due to this adverse event (AE), we had to prematurely euthanized all females in high-dose group at week 6 and subsequently exclude them from the data analysis of blood LPS concentration and immunophenotyping for the last two timepoints. All animals from low- and mid-dose group, as well as males from high-dose group had gradual weight gain over time and showed no sign of pain, stress or AE (Figure 4C,D).

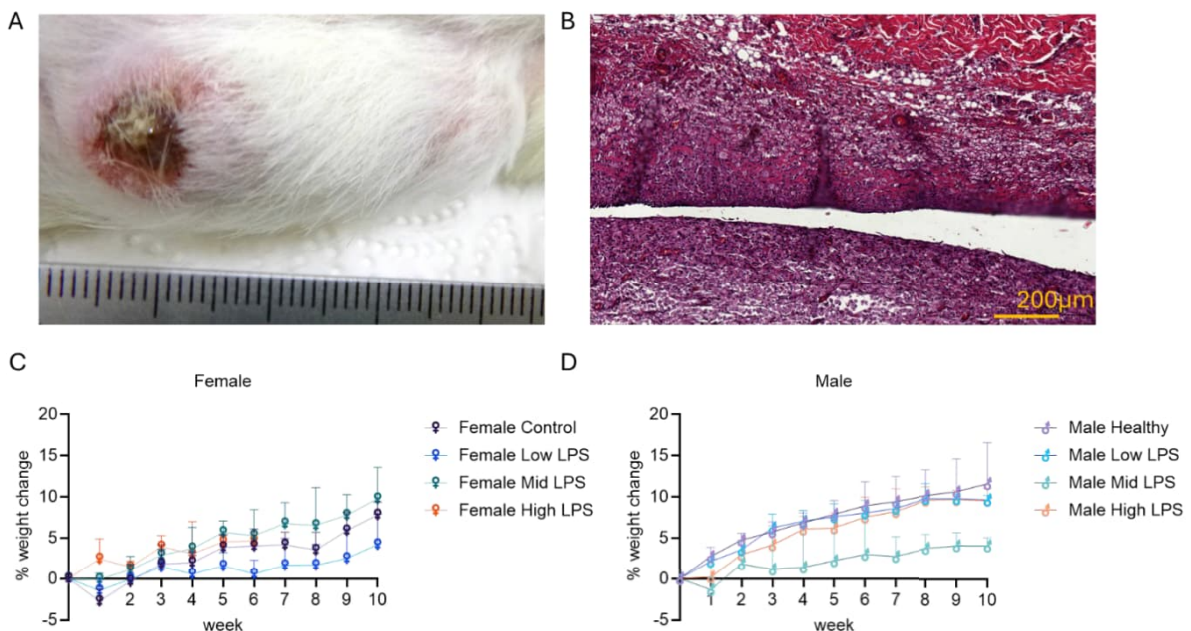


Figure 4. The safety of systemic administration of LPS.

Macroscopic view (A) and HE staining (B) of skin ulcers developed in females from High-LPS group. Scale bar: 200µm. Percentage of weight change over time for (C) females and (D) males.

### 3.1.2 Plasma LPS concentration and peripheral immune cell population

For females, despite large sample variation, continuous systemic administration of LPSs could elevate the plasma LPS concentration. Low-LPS group had significantly higher plasma LPS compared to No-LPS controls at day 46 and day 60. However, plasma LPS concentration did not differ between any of the treatment groups for the males (Figure 5).

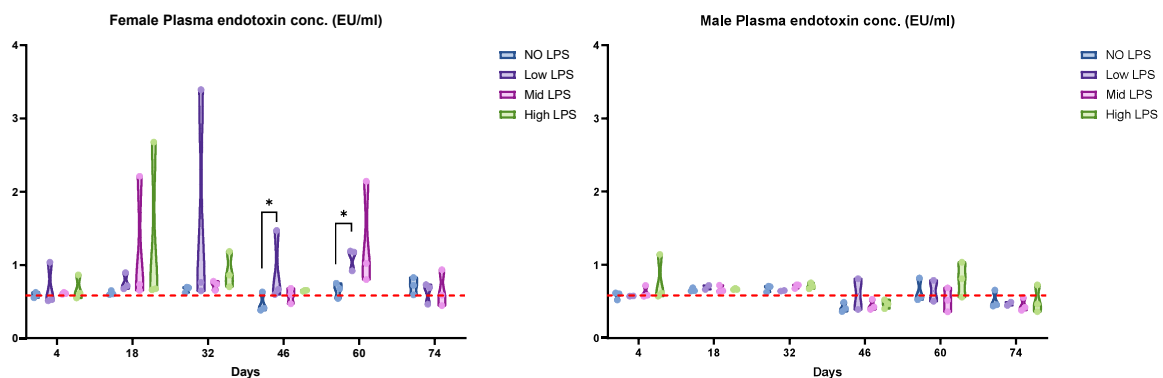


Figure 5. Plasma LPS concentration.

Violin plot showing data distribution. Red dotted line indicates the value of No LPS group at day 4. \*  $P < 0.05$ .  $N = 2 - 3$  per group.

Immunophenotyping showed that the percentage of monocytes and neutrophils in peripheral blood were rapidly elevated in response to LPS as early as day 4 in both females and males (Figure 6). Low- and mid-dose of LPS were sufficient to induce significant increase of monocytes and neutrophils population compared to no LPS control in female animals (Figure 6A, C). However, statistically significance was only observed between controls and mid- or high-LPS groups in male animals. For this reason, animals from different LPS dosing group were combined for further knee analysis,

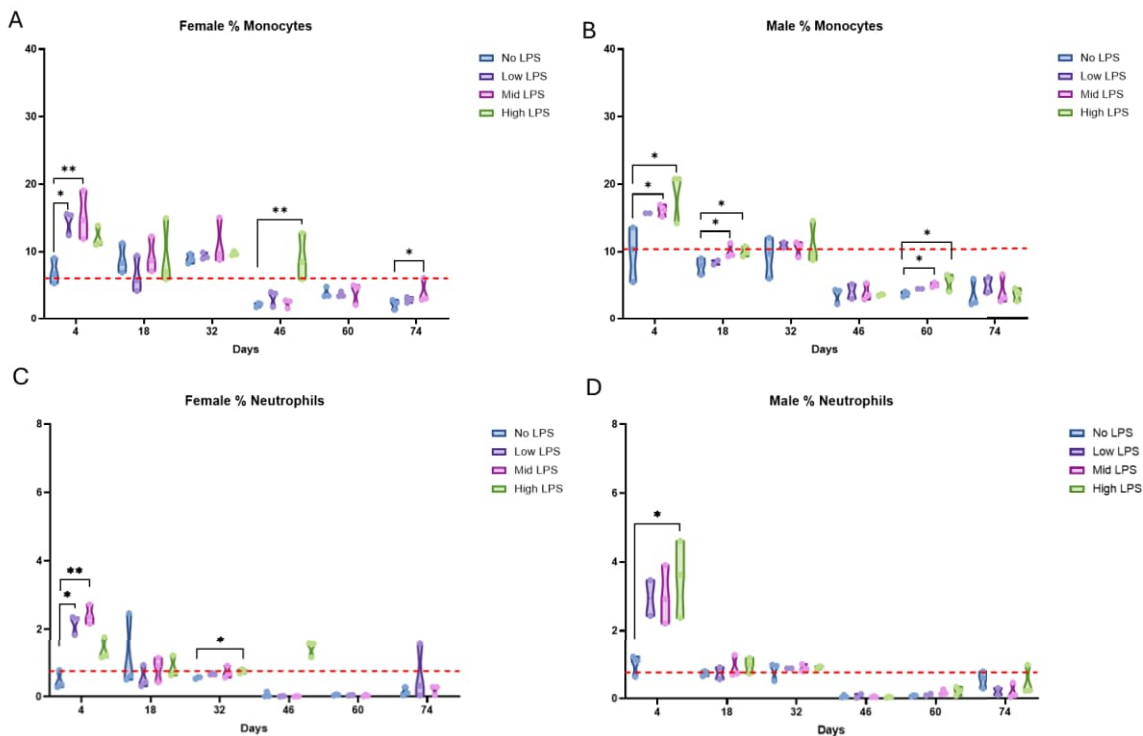


Figure 6. The effect of systemic LPS on peripheral immune cell population. Percentage of monocytes of females (A) and males (B). Percentage of neutrophils of females (C) and males (D). Violin plot showing data distribution. Red dotted line indicates the value of No LPS group at day 4. \*  $P < 0.05$ . \*\*  $P < 0.01$ .  $N = 2 - 3$  per group.

### 3.1.3 Detection of LPS in knee and effect of LPS on knee

Systemically delivered LPS was detected in the knee by Immunofluorescence staining, with higher synovial fluid endotoxin concentration in LPS group compared to that in control group ( $0.11 \pm 0.05$  EU/ml vs  $0.07 \pm 0.01$  EU/ml,  $p = 0.018$ ) (Figure 7A). Despite higher LPS level in the blood circulation and joints, histological assessments demonstrated no significant synovitis (Figure 7B) or cartilage damage in LPS-treated rats as evidenced by Saf-O staining (Figure 7C) [5]. The machine learning-assisted microCT analysis provided unbiased and high-resolution of cartilage surface roughness (CRS) of the whole cartilage (Figure 7D). Based on microCT analysis, LPS-treated females showed higher CRS score in medial tibia plateau (MTP) region compared to No-LPS control females. Male animals showed comparable cartilage surface roughness between LPS and control group in all regions of the knee (Figure 7E).

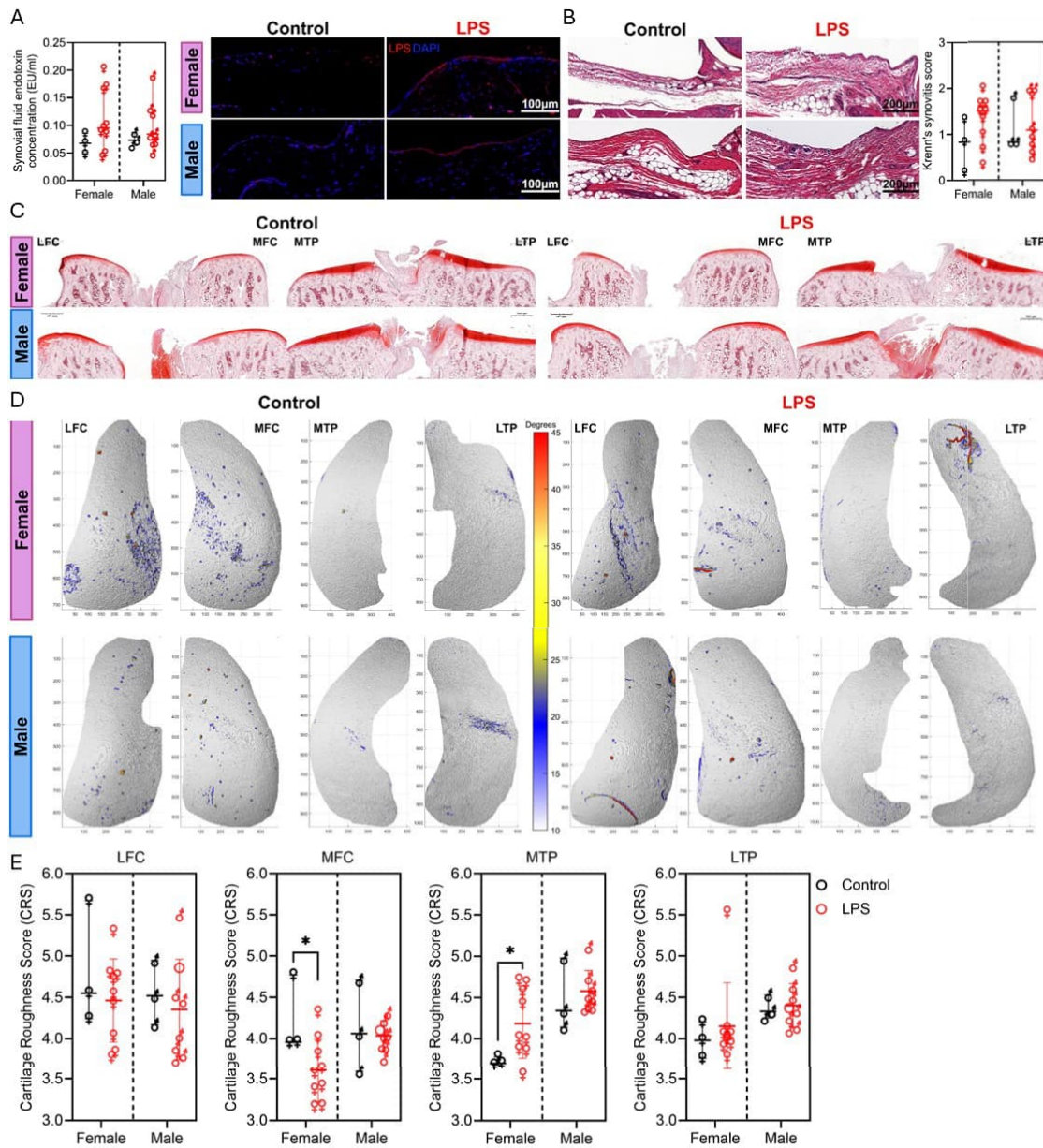


Figure 7. The effect of LPS on female and male knee joints.

(A) Synovial fluid LPS concentration and Immunofluorescence staining of E. Coli LPS on knee synovial membranes. Data represented as median ± 95% confidence interval (CI). (B) HE staining of knee synovial membrane and Krenn's synovitis score. (C) Saf-O of the knee medial tibia plateau (MTP). (D) Representative microCT surface roughness maps and (E) cartilage roughness score of lateral femoral condyle (LFC), medial femoral condyle (MFC), medial tibia plateau (MTP) and lateral tibia plateau (LTP). Data represented median ± 95% CI. N = 3 for no LPS controls (Control group), and N = 9 for LPS-treated animals (LPS group).

## 3.2 COMPARISON BETWEEN SYSTEMIC AND INTRA-ARTICULAR LPS

### 3.2.1 Cartilage integrity and matrix degradation

Histological assessment of knee joints revealed that both systemic and intra-articular LPS exposure induce some cartilage degeneration compared to controls (Figure 8A). Systemic LPS administration resulted in slight loss of cartilage matrix and chondrocytes in the MTP region with changes being more pronounced in females as shown in the OARSI CDS (Figure 8B). Intra-articular LPS produced greater degree of cartilage damage relative to systemic exposure, as evidenced by TB staining. The trend was further confirmed by CDS score (Figure 8B).

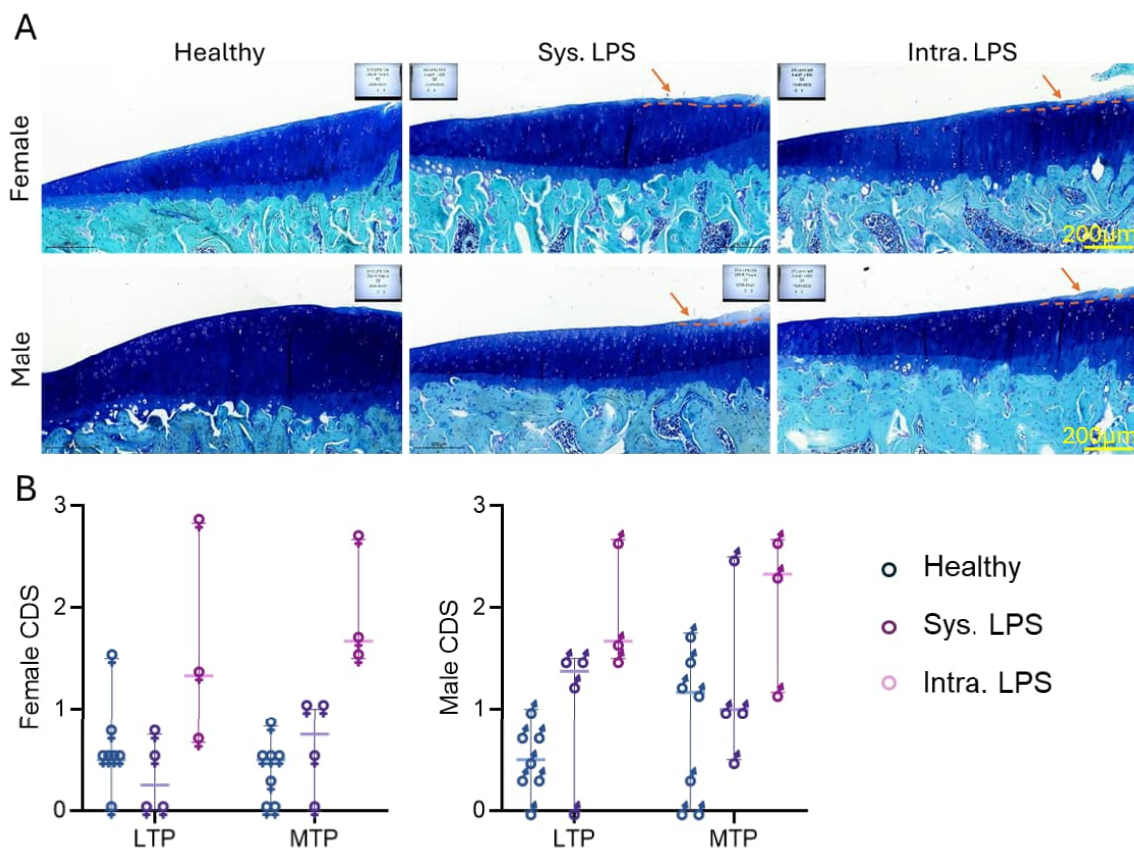


Figure 8. Effect of systemic and intra-articular LPS on cartilage matrix degeneration. (A) Representative images of MTP region of the knee joints stained with TB staining. Yellow arrows indicate area of cartilage degeneration, and dotted line marks the boundary of degenerative cartilage. Scale bar: 200µm. (B) OARSI cartilage degeneration score (CDS) for LTP and MTP region of the knee. Healthy: No LPS control animals. Sys. LPS: Animals receiving systemic LPS administration. Intra. LPS: animals

receiving intra-articular LPS injection. Data represented median  $\pm$  95% CI. N = 3 – 7 rats per group.

### 3.2.2 Cartilage surface roughness

CRS score computed by microCT analysis indicated that systemic LPS exposure led to subtle changes in the cartilage surface integrity in the MTP region of female knee, which is consistent with histological finding (Figure 9B). On the contrary, intra-articular injections of LPS did not induce significant changes in surface regularity when compared to control animals for both sexes (Figure 9).

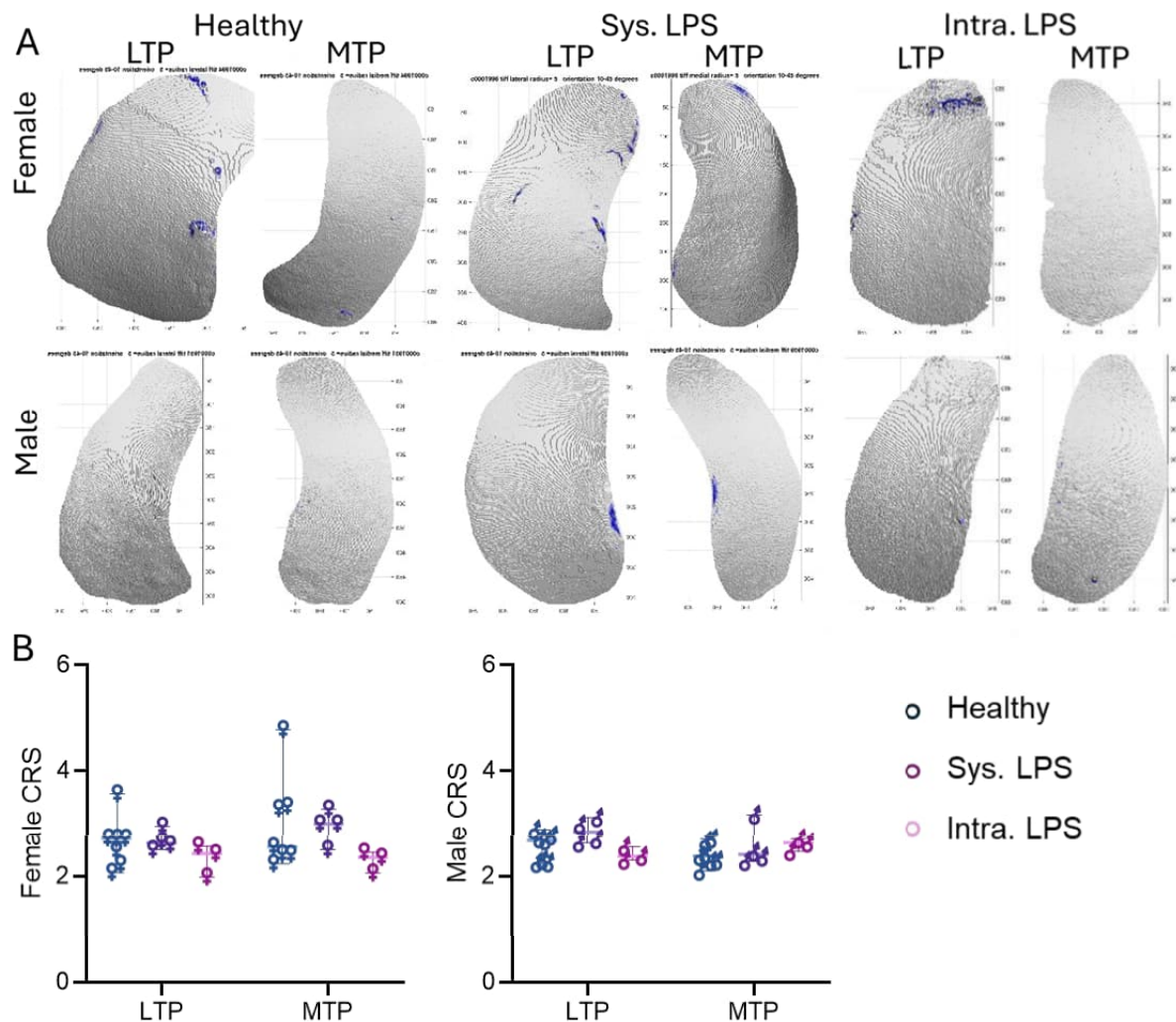


Figure 9. Effect of systemic and intra-articular LPS on cartilage surface roughness. (A) Representative microCT surface roughness maps and (B) cartilage roughness score of medial tibia plateau (MTP) and lateral tibia plateau (LTP). Healthy: No LPS control animals. Sys. LPS: Animals receiving systemic LPS administration. Intra. LPS: animals receiving intra-articular LPS injection. Data represented median  $\pm$  95% CI. N = 3 – 7 rats per group.

### 3.2.3 Synovial membrane inflammation

Despite comparable cartilage degeneration, systemic and intra-articular LPS differed markedly in their effects on synovial inflammation (Figure 10A). Systemic LPS exposure resulted in minimal synovitis measured by Krenn’s synovitis score, with synovial lining thickness, immune cell infiltration remaining close to healthy controls in both sexes (Figure 10B). In contrast, intra-articular LPS significantly elevated synovial inflammation by promoting synovial hyperplasia and immune cell infiltration, leading to a much higher total Krenn’s score compared to control and systemic LPS group (Figure 10B). Interestingly, intra-articular LPS induced more pronounced local immune activation and synovial inflammation in males compared to females.

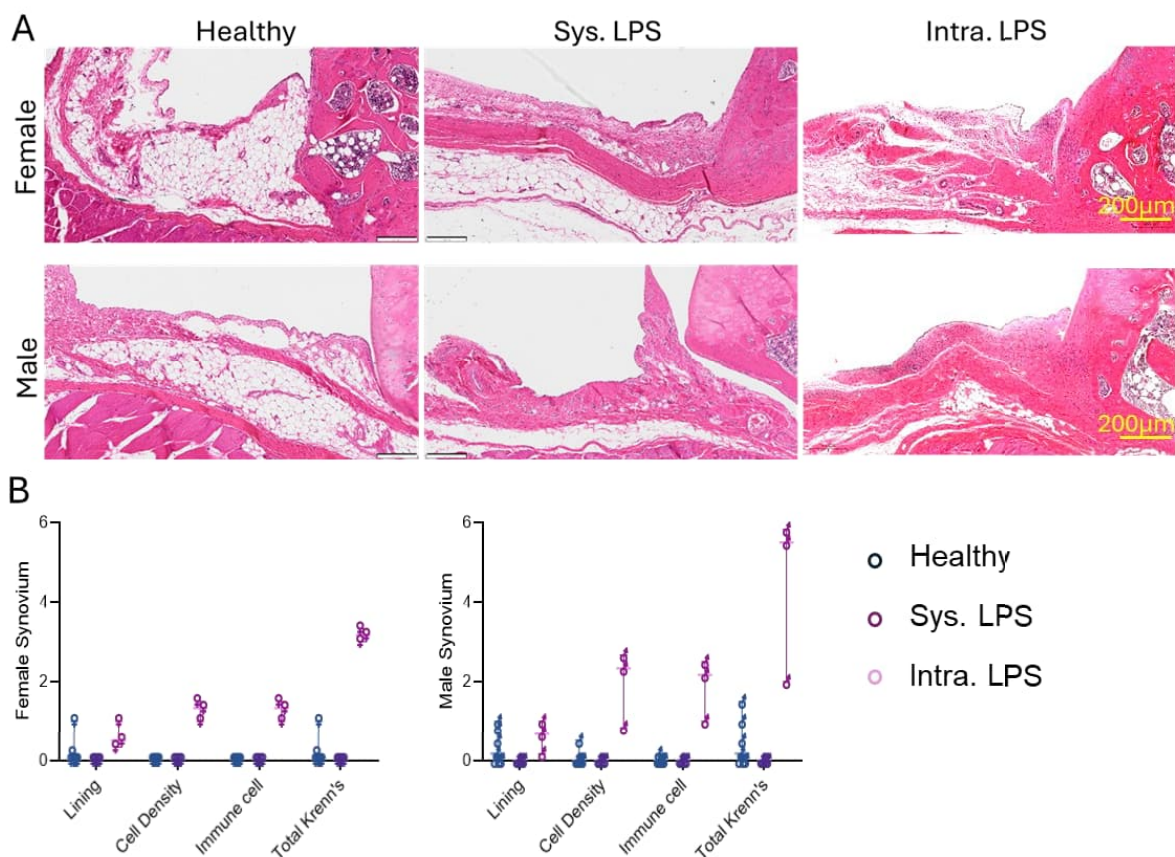


Figure 10. Effect of systemic and intra-articular LPS on synovitis.

(A) Representative HE images of synovial membrane. Scale bar: 200µm. (B) Sub-categorical and total krenn’s score of synovial membrane. Healthy: No LPS control animals. Sys. LPS: Animals receiving systemic LPS administration. Intra. LPS: animals receiving intra-articular LPS injection. Data represented median ± 95% CI. N = 3 – 7 rats per group.

## 4. CONCLUSION

The experimental results presented in Deliverable 3.4 demonstrate that LPS exposure influences the severity of arthritic disease in a rat model in a manner dependent on route of administration and sex. Chronic systemic LPS exposure induced elevation of circulating LPS and activation of innate immunity, mild cartilage degeneration with minimal synovial inflammation, whereas intra-articular LPS resulted in more pronounced synovial inflammation and cartilage matrix degeneration.

Sex-dependent differences were observed, with females showing increased sensitivity to systemic LPS and males exhibiting stronger synovial inflammatory responses following intra-articular LPS injections. Together, these findings confirm that LPS can modulate arthritic disease severity in vivo and that systemic and local LPS challenges produce different pathological profiles. This deliverable therefore fulfills its objectives by providing experimental evidence on the role of LPS in arthritic severity in a preclinical rat model.

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