Diabetes Accelerate Bone Loss, Implant Failure, and Infection Persistence in Periprosthetic Joint Infection

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INTRODUCTION: Periprosthetic joint infection (PJI) remains one of the most devastating complications of arthroplasty. Patients with diabetes are disproportionately affected, but the mechanisms linking metabolic disease to infection-driven bone loss and implant failure are not fully defined. Here, we demonstrate a pilot model of (controlled) diabetic joint replacement.

METHODS: Experiments were conducted under MGH IACUC protocol 2022N000108. A total joint arthroplasty was simulated by transchondylarly implanting a 3.0 x 3.0mm cylindrical polyethylene (PE) plug into the distal femur and a titanium screw in the proximal tibia on 2 male Zucker lean and 2 male Zucker diabetic rats. 10µL of Methicillin-sensitive Staphylococcus aureus (MSSA) 10^8 CFU was injected into the tibial canal before screw insertion and 40µL was injected into the joint space before wound closure. Non-surgical Sprague-Dawley rats (n=2) and Zucker obese rats (n=2) served as non-surgical controls. To mitigate hyperglycemia, an insulin pump was inserted dorsally in diabetic rats (n=2), releasing up to 4 IU/day from 5 days before surgery until POD 28. Blood glucose was tested using Bayer Contour Blood Glucose Strips. Quantitative cultures were performed from tibia, femur, screw, and polyethylene (PE) explants to determine bacterial load. RNA-seq profiled $CD4^+/CD8^+$ T cell associated pathways. Longitudinal radiographs (POD 2–28) evaluated peri-implant lucency, migration, and fracture. Micro-CT of a 9 mm metaphyseal region quantified bone volume fraction (BV/TV) and bone marrow density (BMD). H&E staining assessed osteolysis and inflammatory infiltrates. Toe-spread analysis measured functional limb use.

RESULTS SECTION: Blood glucose monitoring confirmed elevated glucose in Zucker diabetic PJI rats (447±6 mg/dL prior to insulin pump implantation, reduced to146.5±80.5 mg/dL with insulin support), while Zucker Obese non-surgical rats showed intermediate elevations (257±12 mg/dL) compared with normoglycemic Zucker Lean PJI controls (87±17 mg/dL). Bacterial cultures demonstrated substantial colony burdens in tibia, femur, screws, and polyethylene (PE) across all infected groups, with diabetic PJI rats showing a trend toward higher counts (6.13×10^6, 1.16×10^8, 1.82×10^7, 6.10×10^5 CFU, respectively) compared with Zucker lean PJI rats (1.95×10^6, 3.07×10^6, 8.50×10^4, 1.03×10^4 CFU). RNA-seq identified downregulation of $CD8^+$ T cell transcripts and altered $CD4^+$ signaling in the diabetic group, consistent with impaired adaptive immunity (**Fig. 1**). RNA-seq volcano plot analysis demonstrated that Zucker diabetic PJI rats, compared with lean PJI rats, exhibited significant downregulation of Cxcl11, Cxcl6, and MMP3, indicating impaired immune cell recruitment and matrix remodeling responses. Radiographs revealed progressive periosteal reaction, radiolucency, and implant migration in infected animals, most severe in the diabetic PJI group. Micro-CT demonstrated reductions in BV/TV and BMD in the cortex of tibia bone in diabetic PJI (60%, 460mgHA/cm^3) and Zucker Lean PJI rats (85%, 656mgHA/cm^3) vs non-surgical Zucker obese (98.51%, 907mgHA/cm^3) and Sprague Dawley non-surgical rats before any intervention (91.4%, 675mgHA/cm^3). H&E showed extensive peri-implant tissue disruption and inflammatory infiltrates, greatest in the diabetic PJI rats (**Fig. 2**). Toe-spread testing revealed marked functional deficits in Zucker Lean PJI and Zucker Diabetic PJI groups (**Fig. 3**).

DISCUSSION: Diabetes amplified infection-driven bone loss, bacterial persistence, immune dysregulation, and functional decline. Diabetes produced the most severe phenotype across all domains. These findings suggest metabolic dysfunction promotes both structural compromise and impaired host defense. While this work represents a pilot study with a modest sample size, it demonstrates the feasibility of using Zucker diabetic rats with insulin pump support to model key traits of diabetes, providing a strong foundation for future studies in larger cohorts and complementary models.

SIGNIFICANCE/CLINICAL RELEVANCE: This study highlights how metabolic disease worsens infection severity, bone loss, and implant failure. Addressing systemic metabolic and immune deficits may improve arthroplasty outcomes in high-risk patients.

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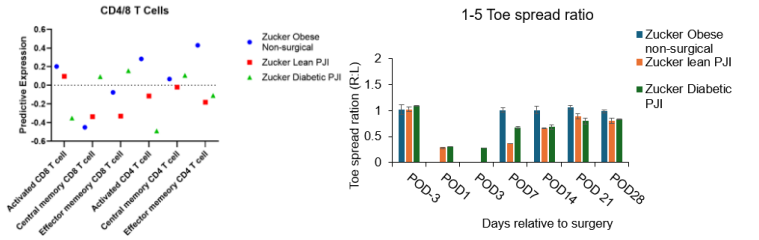

Fig. 1. RNA-seq CD4/CD8 T cell pathway alterations

Fig. 3. toe-spread functional scores.

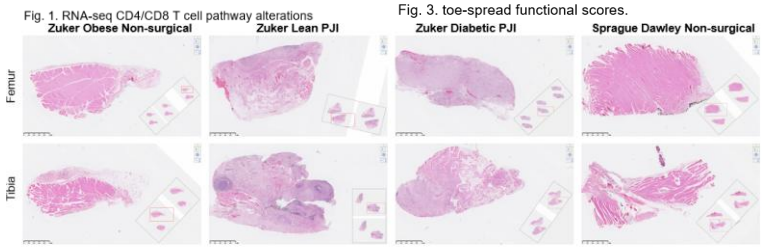

Fig. 2. Representative H&E-stained sections of peri-femur and peri-tibia tissues at POD 28. Zucker obese and Sprague Dawley non-surgical rats showed relatively preserved peri-implant tissue architecture. Lean PJI rats displayed moderate inflammatory cell infiltration and peri-implant tissue disruption. Diabetic PJI rats exhibited extensive dense neutrophil-rich infiltrates within peri-femur and peri-tibia tissues. Arrow bar= 1 mm.