Periprosthetic joint infection is characterized by distinct bone microarchitecture and synovial cytokine profiles.

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INTRODUCTION:
Periprosthetic joint infection (PJI) is one of the most severe complications following joint replacement surgery. While the inflammatory synovial milieu in PJI has previously been investigated, the direct impact on local bone microstructure remains poorly defined. This study aimed to characterize bone quality and synovial cytokine profiles in PJI compared with aseptic revision (AR) surgery and primary osteoarthritis (OA).

METHODS:
We included patients undergoing surgery for PJI (n=52; 32 male, 20 female), AR (n=32; 13 male, 19 female), and OA (n=30; 13 male, 17 female). From these cohorts, femoral bone specimens were obtained intraoperatively for histomorphometry and quantitative backscattered electron imaging (qBEI). Synovial fluid was collected and analyzed using a focused bone and inflammatory multiplex assay. Statistical analysis included one-way ANOVA with Tukey post hoc testing. This study was approved by the institutional Ethics Committee, and informed consent was obtained from all participants.

RESULTS:
Histological analyses demonstrated increased local bone mass in PJI compared with AR and OA, while mineralization density distribution parameters (CaMean, CaPeak, CaWidth) showed no differences. Cellular analyses revealed significantly elevated osteoblast and osteoclast numbers in PJI compared with AR and OA ($p<0.001$). Synovial fluid analysis showed markedly elevated IL-6 in PJI compared with AR ($p<0.001$). Sclerostin was increased in PJI compared with AR ($p=0.043$), while osteoprotegerin and osteocalcin were lower in PJI compared with OA ($p<0.001$).

DISCUSSION:
This study provides evidence of microstructural and molecular alterations in the bone microenvironment of PJI. The combination of increased bone mass and markedly elevated osteoclast numbers suggests a paradoxical remodeling phenotype, in which infection drives both osteosclerotic and osteolytic processes. Such concurrent changes highlight the complexity of infection-induced bone adaptations, where reactive bone formation coexists with heightened resorption. Cytokine profiling further delineates this distinct inflammatory milieu, characterized by IL-6 elevations, which indicate a robust pro-inflammatory state that promotes osteoclastogenesis, while elevated sclerostin and reduced osteoprotegerin and osteocalcin levels suggest dysregulated bone signaling and impaired turnover balance. Notably, AR patients did not share the same cytokine profile as PJI, underscoring that aseptic conditions (i.e., loosening, instability) and infection represent biologically distinct entities despite converging on implant failure. Overall, these findings underscore the dual impact of PJI on bone structure and inflammatory signaling. The presence of increased bone mass, enhanced osteoclastic activity, and elevated pro-inflammatory cytokines suggests that infection destabilizes implants not only through microbial activity but also via profound disruption of local bone homeostasis. This mechanistic insight supports the integration of cytokine profiling into the diagnostic workup of revision arthroplasty. Future studies should validate these markers in larger cohorts and evaluate their potential for guiding risk stratification, therapeutic interventions, and prediction of reinfection or implant failure.

SIGNIFICANCE/CLINICAL RELEVANCE:
This study addresses the critical challenge of PJI by linking bone microarchitecture with synovial cytokine alterations in a unified analysis. PJI was associated with increased bone mass, heightened osteoclastic activity, and a distinct pro-inflammatory cytokine signature dominated by IL-6. These findings provide new insights into infection-driven bone remodeling mechanisms and identify candidate biomarkers that may enhance diagnostic accuracy and support the development of targeted strategies to improve outcomes after revision arthroplasty.