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Inflammation of Bone in Patients with Periprosthetic Joint Infections of the Knee

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Background: Despite the general success of total knee arthroplasty (TKA), addressing periprosthetic joint infection (PJI) and the resulting long-term complications is a growing medical need given the aging population and the increasing demand for arthroplasty. A larger proportion of patients face revision surgery because of the long-term complication of aseptic loosening despite clearance of the infection. The pathomechanisms leading to prosthetic loosening are not understood as it has been widely assumed that the bone stock recovers after explantation revision surgery. While clinical observations suggest a reduced osteogenic potential in patients with PJI, knowledge regarding the relevant biology is sparse. In the present study, we investigated the inflammatory impact of PJI on the bone and bone marrow in the vicinity of the joint. Additionally, we evaluated changes in the local inflammatory environment in a 2-stage exchange at both explantation and reimplantation.

Methods: In this study, we analyzed 75 human bone and bone-marrow specimens (obtained from 65 patients undergoing revision arthroplasty with cement for the treatment of PJI) for markers of inflammation. Samples were analyzed using hematoxylin and eosin overview staining, fluorescent immunohistochemical staining, flow cytometry, and polymerase chain reaction (PCR).

Results: Leukocyte prevalence was significantly elevated at explantation (femur, +218.9%; tibia, +134.2%). While leukocyte prevalence decreased at reimplantation (femur, −49.5%; tibia, −34.2%), the number of cells remained significantly higher compared with the control group (femur, +61.2%; tibia, +54.2%). Expression of inflammatory markers interleukin (IL)-1α (femur, +2,748.7%; tibia, +1,605.9%), IL-6 (femur, +2,062.5%; tibia, +2,385.7%), IL-10 (femur, +913.7%; tibia, +897.5%), IL-12 (femur, +386.1%; tibia, +52.5%), IL-18 (femur, +805.3%; tibia, +547.7%), and tumor necrosis factor (TNF)-α (femur, +296.9%; tibia, +220.9%) was significantly elevated at prosthesis explantation in both femoral and tibial specimens. Expression remained significantly elevated at reimplantation for all inflammatory markers except IL-12 compared with the control group. Conversely, there were only limited inflammatory changes in the bone marrow environment.

Conclusions: The present study demonstrated a strong and lasting upregulation of the proinflammatory environment in the joint-surrounding osseous scaffold in patients with PJI. Our data suggest that modulating the inflammatory environment has substantial potential to improve the clinical outcome in affected patients.

Despite increased use of antibiotics and improved aseptic surgical techniques, periprosthetic joint infection (PJI) still occurs in association with 1% to 5% of primary total knee arthroplasties (TKAs) and thus remains one of the most challenging complications of total joint arthroplasty[1]. In most cases, once a biofilm forms on the implant, complete removal of the infected prosthesis and, in a second-stage procedure, reimplantation of a new prosthesis are necessary[2-4]. After successful surgical treatment, the risks of recurrent PJI and aseptic loosening have been reported to be 5% to 20% and 22%, respectively[5,6], suggesting a potential lasting impact of PJI on bone metabolism. Although the pathomechanisms responsible for aseptic loosening are subject to ongoing debate, the involvement of osteoimmunological pathways has been suggested to play a vital role in disease progression[6,7]. However, the pathomechanism responsible for the increased occurrence of

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long-term prosthesis failure after revision surgery for PJI is unknown[6]. In particular, there is a paucity of knowledge regarding the impact of PJI on the inflammatory environment in bone and its potential impact on the regenerative capabilities after treatment with antibiotics and after surgically addressing the infection.

Inflammation has been shown to impact the regenerative capabilities of bone through various proinflammatory cytokines (i.e., interleukin [IL]-1, IL-6, IL-10, IL-12, and tumor necrosis factor [TNF]-α[8-10]). While an initial proinflammatory environment has been indicated as pivotal for bone regrowth and remodeling in patients with various pathologies, prolonged inflammation can inhibit remodeling, can delay bone-healing, and may lead to insufficient implant integration[11,12]. Deficiency in expression of these inflammatory cytokines has been demonstrated to negatively impact bone neovascularization, bone matrix formation, and osteoblast and osteoclast activation[8,13]. Conversely, overexpression of these cytokines can lead to systemic bone loss and decreased regenerative capacities of bone[14].

Previous research has mainly focused on reliably diagnosing PJI with use of serum, synovial fluid, and intraoperatively collected implants[15,16]. Several authors have identified increased levels of inflammatory cytokines, such as IL-6, in the synovial fluid and serum[15,17,18]. However, the inflammatory impact of PJI on the surrounding skeletal system, namely, on local cytokine levels and immune system cells, remains an open question. It is unknown if the potential presence of inflammatory cytokines also plays a key role in the regeneration of bone and osteointegration of the new implant in patients with this pathology. Alterations in clinical outcome after revision arthroplasty for PJI may be largely dependent on the local inflammation of bone and bone marrow.

In the present study, we analyzed 75 human bone and bone-marrow specimens (obtained from 65 patients undergoing revision arthroplasty with cement for the treatment of PJI) for markers of inflammation.

Material and Methods

Patients

The present study was approved by the Charité University Hospital ethics board (EA2/083/19) and was completed in accordance with the Declaration of Helsinki. All patients undergoing exchange of a total knee replacement because of PJI between January 1, 2020, and June 1, 2022, at the Charité University Hospital in Berlin, Germany were eligible for this study. Patients were treated in a specialized department with use of a centralized and interdisciplinary treatment approach. Patients undergoing TKA for the treatment of primary osteoarthritis were used as the control group. PJI was defined according to the European Bone and Joint Infection Society (EBJIS) criteria[19]. The exclusion criteria included (1) HIV (human immunodeficiency virus), (2) osteoporosis, (3) infection of a native knee joint without a prosthesis, and/or (4) treatment with primary TKA because of trauma or infection. There were no other exclusion criteria. TKA reimplantation was performed at least 6 weeks after implant removal in patients who did not present with any clinical or paraclinical signs of persisting infection.

We analyzed 75 intraoperatively acquired femoral, tibial, and bone-marrow specimens from a total of 65 patients. For 10 patients, samples were collected at both explantation and reimplantation. Patients were divided into 3 groups according to the type of surgery: (1) prosthesis explantation (n = 23), (2) prosthesis reimplantation (n = 27), and (3) control (n = 25). Additionally, we performed a subgroup analysis of the 10 patients from whom specimens were acquired at explantation and reimplantation. Demographic data, including age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score, Krenn-Morawietz pathological classification of tissue specimens, and the underlying pathogen, were assessed for all patients.

Sample Preparation

Specimens were obtained intraoperatively from the femur and tibia. At prosthesis explantation, reimplantation, and (for the control group) primary TKA implantation, cubic bone samples of approximately 2 to 3 mm^3 were collected from the distal femoral and proximal tibial bone at the bone-cement interface. Additionally, femoral bone marrow was aspirated in a heparinized tube immediately after surgical access to the bone marrow was established. Samples were immediately stripped of soft tissue, cleaned of blood with use of Ringer solution (B. Braun), and placed in 4% paraformaldehyde (PFA) for histological analysis or in RNAlater solution (Ambion) for polymerase chain reaction (PCR).

Histological Staining

Bone specimens underwent histological staining to provide an overview and to assess changes in bone structure and cell prevalence. Samples were first fixed in 4% PFA for 48 hours and then decalcified in EDTA (ethylenediaminetetraacetic acid) solution (Carl Roth) at 37°C for 4 weeks. After dehydration in an automatic sample processor (Leica TP1020; Leica Biosystems), samples were embedded in paraffin and were prepared as 4-μm-thick sections with use of a manual rotary microtome (Leica RM2235; Leica Microsystems). Sections were stained with Papanicolaou solution 1a Harris hematoxylin (Merck) and eosin (Chroma Waldeck). Mosaic images at 20× magnification were made with use of a Leica DM6B microscope (Leica Microsystems). Where applicable, representative images were chosen.

Fluorescent Immunohistochemical Staining

To further evaluate the occurrence of specific cell populations, fluorescent immunohistochemical staining was performed. After overnight fixation in 4% PFA, bone specimens were embedded in SCEM medium (Section Laboratory) and frozen over cooled hexane (Carl Roth). With use of a cryotome (Leica CM3050S; Leica Microsystems), 7-μm-thick sections were cut, and the sections were mounted on microscope slides with use of cryofilm (Cryofilm type II C; Section Laboratory). After

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TABLE I Patient Characteristics

	Control Group (N = 25)			PJI Group							
				Explantation (N = 23)				Reimplantation (N = 27)			
Characteristic	No. of Patients	Mean	Range	No. of Patients	Mean	Range	P Value	No. of Patients	Mean	Range	P Value
Age *(yr)*		69.8	54.0-87.0		69.3	49.0-91.0	0.420		68.2	49.0-85.0	0.266
Sex							0.083				0.096
Male	9			15				17			
Female	16			8				10			
BMI *(kg/m²)*		28.5	22.1-36.7		30.1	24.7-43.6	0.097		29.2	20.4-43.6	0.282
ASA score							0.227				0.177
1	3			0				0			
2	16			14				16			
3	6			8				10			
4	0			1				1			

blocking with 5% FCS (fetal calf serum) and 1% BSA/TBS (bovine serum albumin in Tris-buffered saline), specimens were stained overnight at 4°C for CD33 (1:100) (304052; ThermoFisher Scientific) and CD45 (1:100) (11-0338-42; BioLegend). Sections were mounted in Fluoromount-G with DAPI (4′,6-diamidino-2-phenylindole) (SouthernBiotech). Second-harmonic-generation microscopy was used to visualize collagen fiber bundles. Mosaic images at 20× magnification were made with use of a Leica DM6B microscope (Leica Microsystems). Where applicable, representative images were chosen.

Flow Cytometry

The cell-population composition of bone-marrow specimens was assessed with use of flow cytometry. After blocking of bone-marrow specimens with use of Fc blocking reagent (BioLegend), samples were stained for leukocytes with anti-CD45 antibody (1:50) (304047; BioLegend). Red blood cells were removed with use of lysis buffer (ThermoFisher Scientific). After fixation with 2% PFA, cells were kept in darkness at 4°C until analysis. Data were acquired with use of an LSRFortessa flow cytometer (BD Biosciences) and were analyzed with use of FlowJo software (V10.6.2; BD Biosciences).

Gene Expression Analysis

PCR was employed to investigate the expression of inflammatory cytokines. After isolation with use of an RNeasy Mini Kit (Qiagen), RNA was transcribed into cDNA with use of a RevertAid First Strand cDNA Synthesis Kit (ThermoFisher Scientific). Following real-time quantitative polymerase chain reaction (RT-qPCR) (7900HT Fast Real-Time PCR System; Applied Biosystems), gene expression was calculated as the fold change in expression. GAPDH (glyceraldhyde-3-phosphate dehydrogenase) was used as a housekeeping gene.

Statistical Analysis

All data were collected and recorded with use of Excel 2016 (Microsoft). Where applicable, data are presented as the mean or median and were analyzed for significance with use of the Student t test or the Mann-Whitney U test. All statistical analyses and plotting were performed with use of R software

TABLE II Krenn-Morawietz Classification and Pathogens in Patients with PJI

	No. of Patients (N = 23)
Krenn-Morawietz classification	
1	2 (8.7%)
2	10 (43.5%)
3	7 (30.4%)
4	3 (13.0%)
Not available	1 (4.3%)
Pathogen	
Staphylococcus aureus	5 (21.7%)
Staphylococcus epidermidis	4 (17.4%)
Staphylococcus hominis	3 (13.0%)
Cutibacterium acnes	2 (8.7%)
Actinomyces turicensis	1 (4.3%)
Enterococcus faecalis	1 (4.3%)
Klebsiella oxytoca	1 (4.3%)
Staphylococcus capitis	1 (4.3%)
Staphylococcus haemolyticus	1 (4.3%)
Streptococcus anginosus	1 (4.3%)
Streptococcus dysgalactiae	1 (4.3%)
Streptococcus salivarius	1 (4.3%)
Streptococcus sanguinis	1 (4.3%)
Staphylococcus sciuri	1 (4.3%)
Peptostreptococcus anaerobius	1 (4.3%)

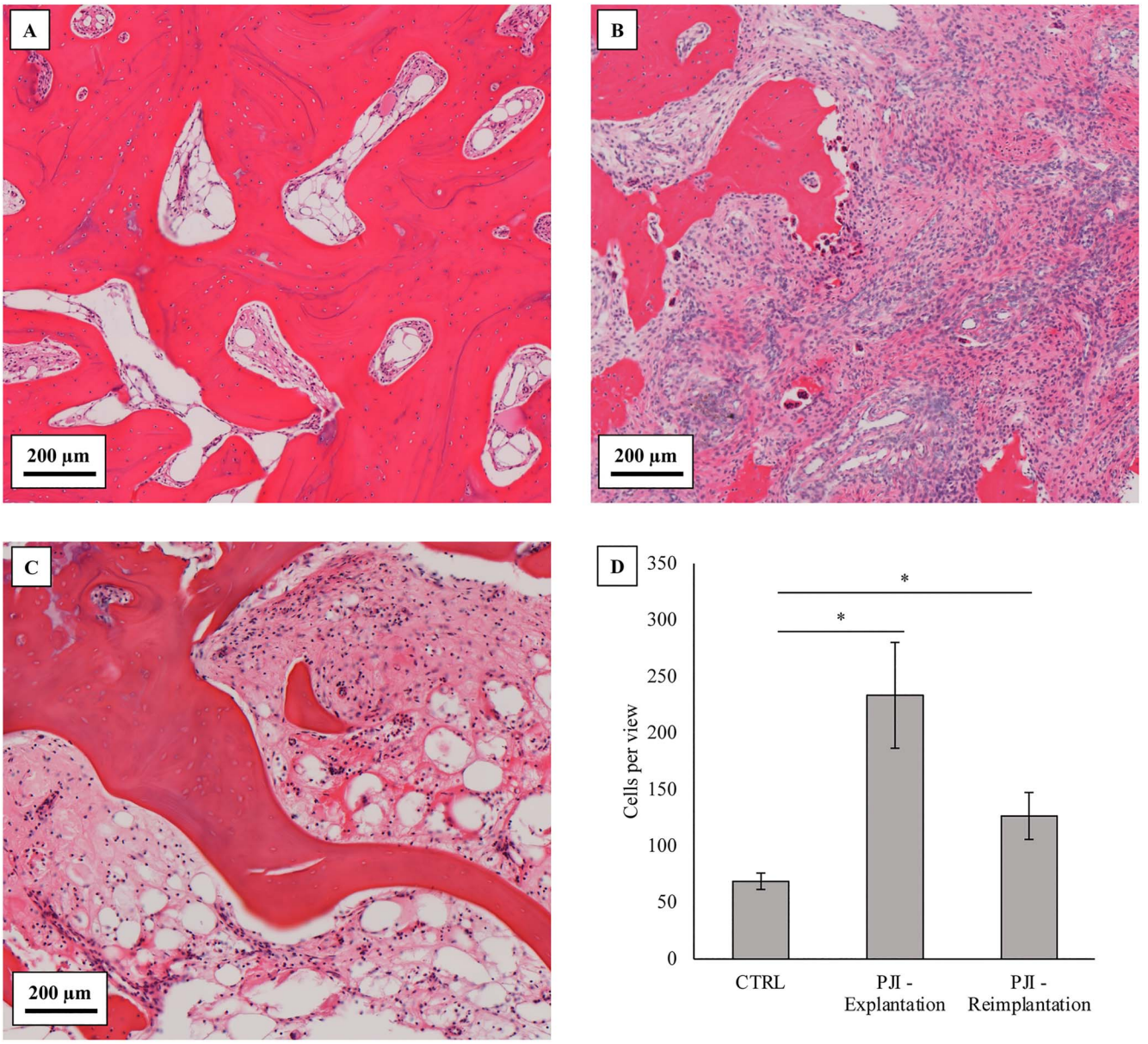

Fig. 1

Figs. 1-A, 1-B, and 1-C Photomicrographs of bone specimens (hematoxylin and eosin). **Figs. 1-A and 1-B** Decreased bone mass and increased cell numbers were observed at prosthesis explantation when patients with PJI (**Fig. 1-B**) were compared with the control group (**Fig. 1-A**). **Fig. 1-C** While cell numbers were no longer as prominently increased at prosthesis reimplantation, they remained significantly elevated. **Fig. 1-D** Bar graph illustrating the quantification of cell numbers. Values are shown as the mean and standard deviation. *Significant difference ($p < 0.05$).

(version 3.6.3; R Development Core Team). The level of significance was set at $p < 0.05$.

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Results

Patients

Patient characteristics are outlined in Table I. Of the patients analyzed in this study, 53.8% were male and 46.2% were female. The mean age at the time of surgery was 69.1 years. The mean BMI was 29.2 kg/m^2. Ninety-five percent of

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all patients had >1 comorbidity. The median ASA score was 2. There were no significant differences in any of the analyzed clinical and paraclinical characteristics between the patients in the control group and those with PJI (at either explantation and reimplantation). In the PJI group, most patients had a Krenn-Morawietz classification of 2 (43.5%) or 3 (30.4%) (Table II). *Staphylococcus aureus, S. epidermidis,* and *S. hominis* were the most common pathogens, comprising 52.1% of all cases.

Cellular Inflammatory Response

Hematoxylin and eosin staining of intraoperatively obtained femoral bone specimens showed significantly increased cell numbers in patients with PJI at explantation compared with the control group (+229%; p = 0.034) (Fig. 1). At reimplantation, cell numbers remained at significantly elevated, albeit lower, levels (+84%; p = 0.025); however, more areas with adipose tissue were observed at that time point. In patients with PJI, CD45+ cell counts were significantly elevated at explantation (femur, +218.9% [p = 0.001]; tibia, +134.2% [p = 0.014]). While CD45+ cell counts significantly decreased at reimplantation (femur, −49.5% [p = 0.009]; tibia, −34.2% [p = 0.048]), the number of cells remained significantly higher compared with the control group (femur, +61.2% [p = 0.040]; tibia, +54.2% [p = 0.049]) (Figs. 2-A through 2-D). Of the leukocytes present, a large number were also positive for CD33, a cell-surface protein on granulocytic myeloid-derived suppressor cells. CD33+ leukocyte cell numbers were significantly elevated both at explantation (femur, +668.9% [p = 0.002]; tibia, +643.4% [p = 0.048]) and reimplantation (femur, +398.7% [p = 0.009]; tibia, +221.5% [p = 0.023]) (Fig. 2-E). In contrast, no significant differences in leukocyte cell numbers were found in bone-marrow specimens (Fig. 3).

Inflammatory Cytokine Expression

At prosthesis explantation, mean expression was significantly elevated for IL-1α (femur, +2,748.7% [p < 0.001; tibia, +1,605.9% [p = 0.001]), IL-6 (femur, +2,062.5% [p = 0.001]; tibia, +2,385.7% [p < 0.001]), IL-10 (femur, +913.7% [p < 0.001]; tibia, +897.5% [p = 0.008]), IL-12 (femur, +386.1% [p = 0.022]; tibia, +52.5% [p = 0.049]), IL-18 (femur, +805.3% [p < 0.001]; tibia, +547.7% [p = 0.001]), and TNF-α (femur, +296.9% [p = 0.001]; tibia, +220.9%

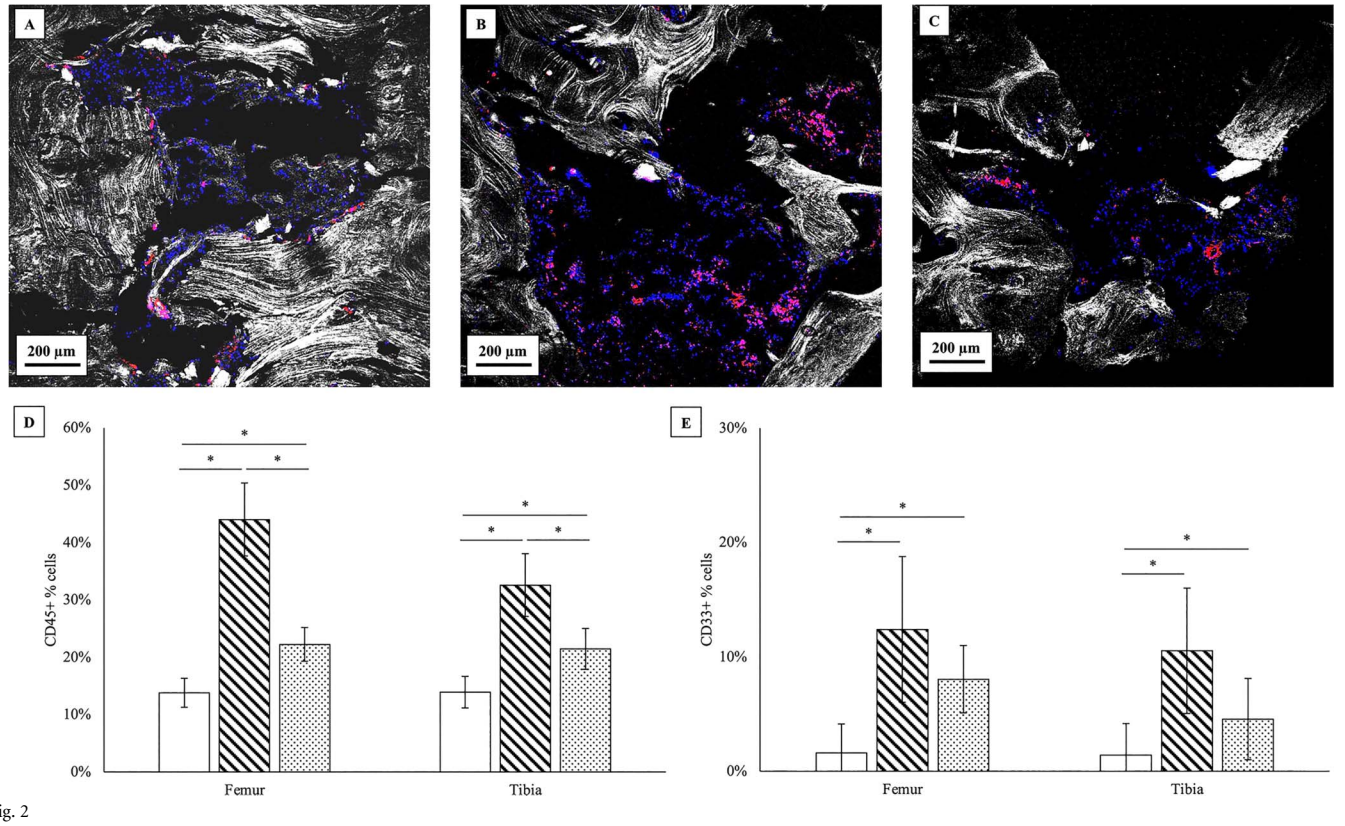

Fig. 2

Figs. 2-A, 2-B, and 2-C Second-harmonic-generation (SHG) photomicrographs of immunohistochemically stained sections of bone specimens from patients in the control group (**Fig. 2-A**) and patients with PJI at both prosthesis explantation (**Fig. 2-B**) and prosthesis reimplantation (**Fig. 2-C**). Blue indicates the nucleus, red indicates CD45, and white indicates collagen fiber bundles. **Figs. 2-D and 2-E** Bar graphs illustrating quantification of CD45+ (**Fig. 2-D**) and CD33+ cell numbers (**Fig. 2-E**) in both femur and the tibia in the control group (white bar), the PJI group at prosthesis explantation (striped bar), and the PJI group at prosthesis reimplantation (dotted bar). Values are shown as the mean and standard deviation. *Significant difference (p < 0.05).

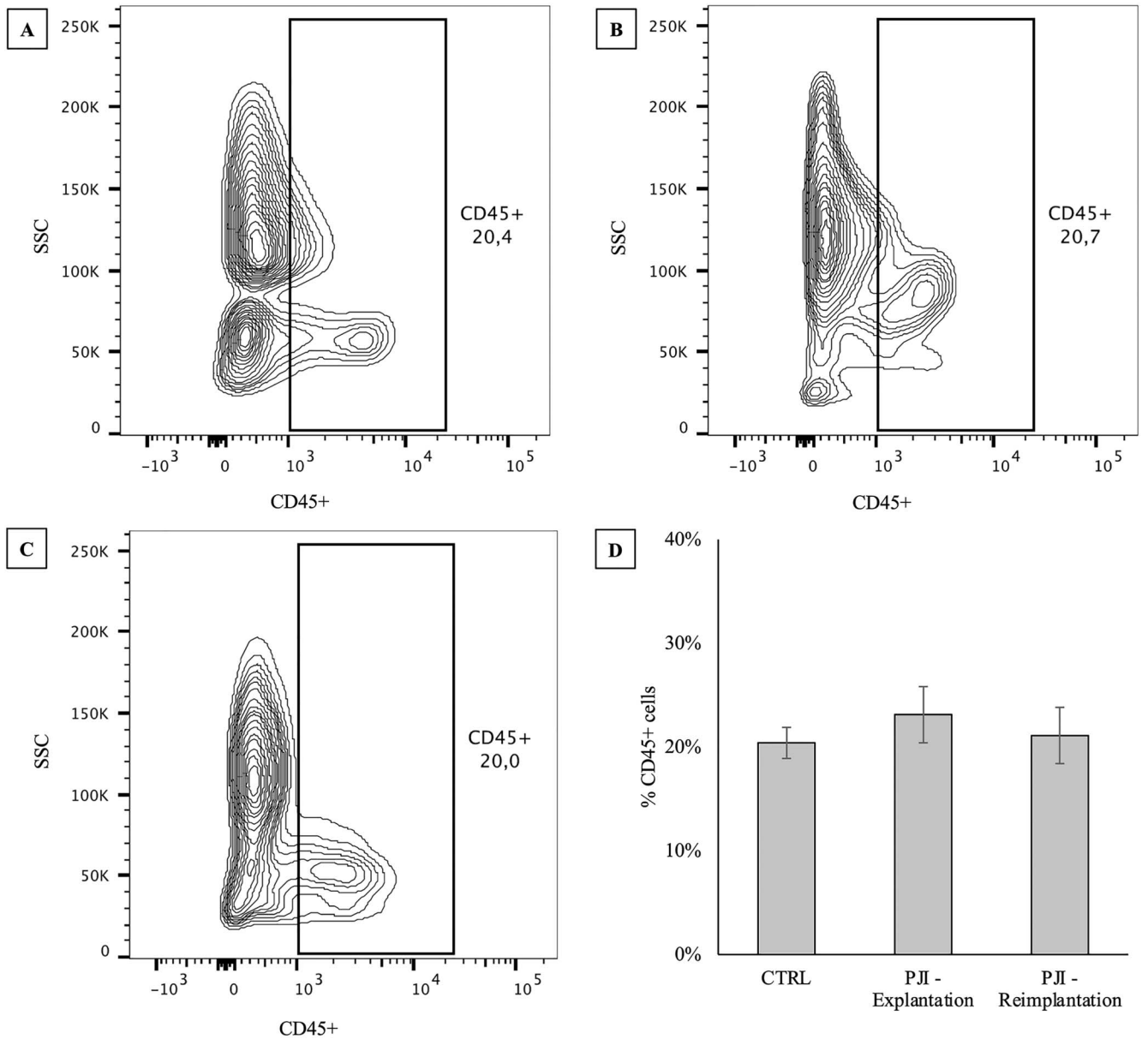

Fig. 3

Figs 3-A, 3-B, and 3-C Flow cytometry analysis of bone-marrow specimens from patients in the control group (**Fig. 3-A**) and patients with PJI at both prosthesis explantation (**Fig. 3-B**) and prosthesis reimplantation (**Fig. 3-C**). SSC = Side Scatter. **Fig. 3-D** Bar graph showing the quantification of CD45+ cell numbers. Values are shown as the mean and standard deviation.

[p = 0.002]) (Fig. 4). At reimplantation, mean expression was only significantly reduced for IL-1α (femur, −80.7% [p = 0.020]; tibia, −61.8% [p = 0.012]), IL-6 (tibia, −64.6% [p = 0.002]), and IL-10 (tibia, −51.4% [p = 0.049]) compared with the level at explantation. However, expression remained significantly elevated for all inflammatory markers except IL-12 compared with the control group. In contrast, in bone-marrow specimens, mean expression of these markers was less elevated, with significantly elevated values being found for only IL-10 (at explantation, +286.0% [p = 0.015]; at reimplantation, +348.4% [p = 0.005]), IL-18 (at explantation, +157.5% [p = 0.010]; at reimplantation, +81.7% [p = 0.012]), and TNF-α (at explantation, +158.0% [p = 0.003]; at reimplantation, +67.8% [p = 0.007]).

For 10 patients, intraoperative specimens could be obtained at both prosthesis explantation and reimplantation (Fig. 5). In a majority of the analyzed patients (7 of 10), expression of all inflammatory cytokines fell sharply at reimplantation. Higher expression at reimplantation than at explantation was only found for a few patients, and with limited consistency across cytokines: IL-6 (P7, +38%),

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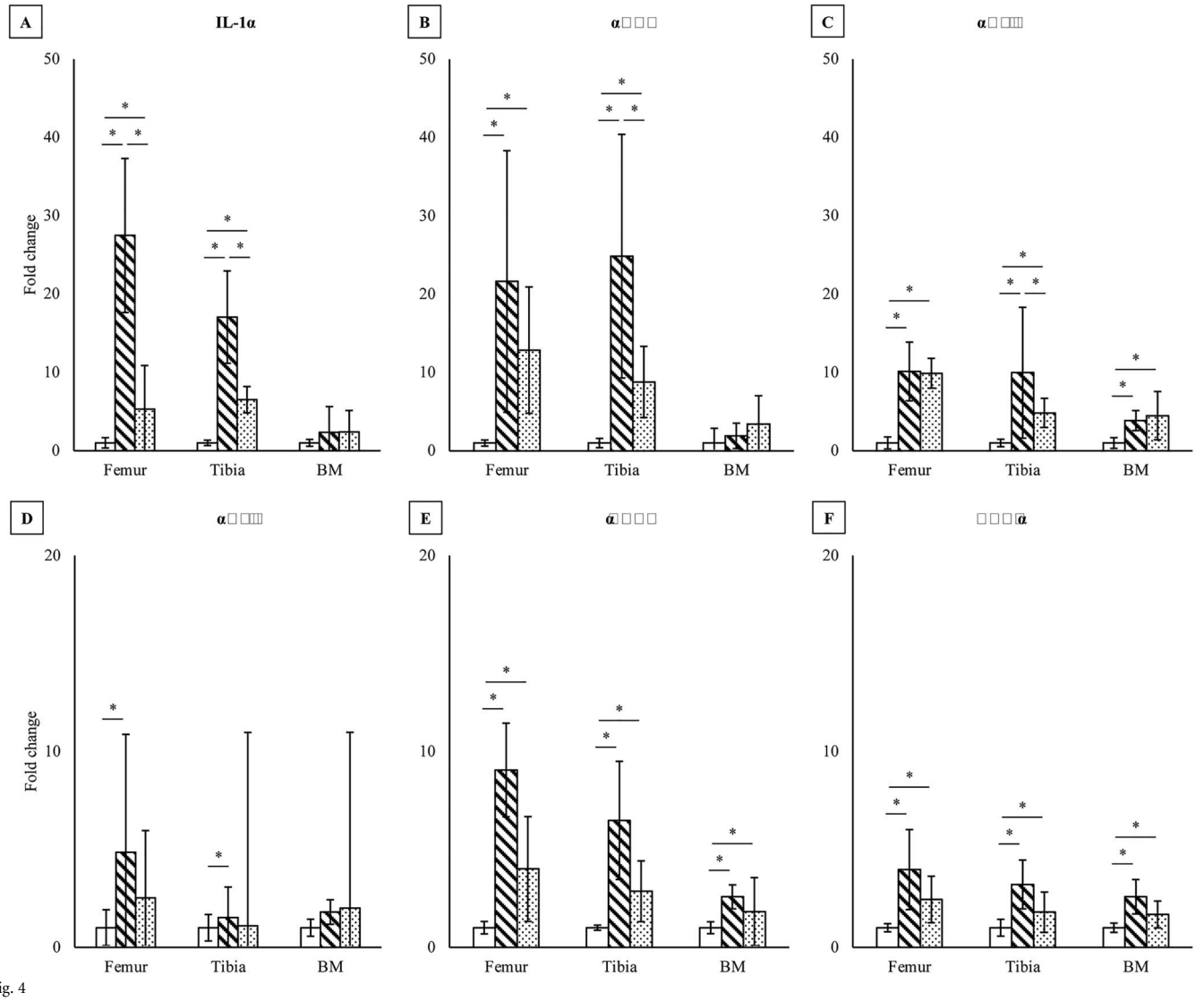

Fig. 4

Figs. 4-A through 4-F Gene expression of inflammatory cytokines IL-1α (**Fig. 4-A**), IL-6 (**Fig. 4-B**), IL-10 (**Fig. 4-C**), IL-12 (**Fig. 4-D**), IL-18 (**Fig. 4-E**), and TNF-α (**Fig. 4-F**) as determined with RT-qPCR in the control group (white bar), the PJI group at prosthesis explantation (striped bar), and the PJI group at prosthesis reimplantation (dotted bar). Values are shown as the mean and standard deviation. *Significant difference ($p < 0.05$). BM = bone marrow.

IL-10 (P2, +77%; P8, +48%), and IL-12 (P7, +171%; P8, +19%).

Discussion

In this study, we investigated the inflammatory impact of PJI on the joint-surrounding bone and bone marrow. Additionally, we evaluated changes in the local inflammatory environment in 2-stage exchange surgery at both explantation and reimplantation. While inflammation was significantly upregulated at explantation due to PJI, the proinflammatory environment was less marked at reimplantation, albeit still significantly elevated compared with the control. Conversely, there were only limited inflammatory changes in the bone marrow environment.

While the pathomechanisms responsible are largely unknown, osteoimmunological pathways in general and a proinflammatory environment in particular have been suggested to be pivotal for disease progression and long-term failure[6,7]. Further evidence of the role of altered bone metabolism is provided by sex-dependent differences, in that women are significantly more at risk for aseptic loosening after PJI revision surgery[20]. To our knowledge, the present study is the first to investigate the effect of PJI on the surrounding skeletal component in humans and to provide evidence of the occurrence of osteitis in the bone surrounding the total knee replacement.

In particular, we found elevated leukocyte infiltration and expression of inflammatory cytokines in the femur and tibia of affected patients. Similarly, a recent study in a murine PJI model demonstrated white blood-cell migration into the bone[21]. Additionally, CD33+ leukocytes (myeloid-derived suppressor cells) were significantly and lastingly elevated. Increased occurrence of

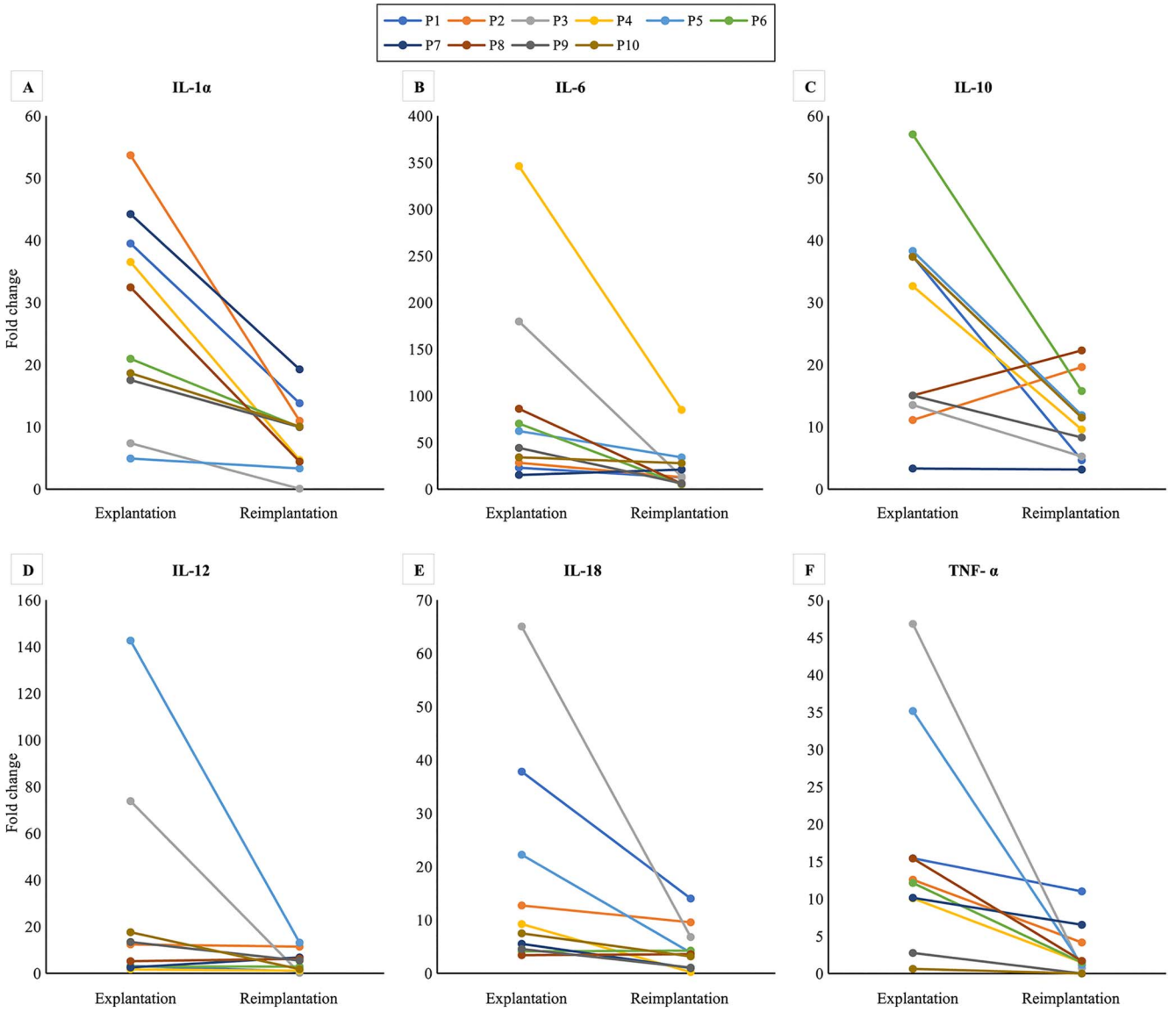

Fig. 5

Figs. 5-A through 5-F Analyses of 10 individual patients (P1 to P10) illustrating gene expression of inflammatory cytokines IL-1α (**Fig. 5-A**), IL-6 (**Fig. 5-B**), IL-10 (**Fig. 5-C**), IL-12 (**Fig. 5-D**), IL-18 (**Fig. 5-E**), and TNF-α (**Fig. 5-F**) at prosthesis explantation and reimplantation as determined with RT-qPCR.

this cell type in the surrounding soft tissue has been associated with an increased risk for chronic infection and may contribute to bone erosion, potentially impacting the long-term clinical outcome[22,23]. We assume that this inflammatory response is mostly driven by the PJI; however, cement and metal particles also need to be evaluated as potential amplifying factors, as they also can induce inflammation[24,25].

While both the presence of white blood cells and the expression of inflammatory cytokines had decreased at reimplantation, all markers except IL-12 remained significantly elevated. For adequate bone regeneration, the timely downregulation of the initial proinflammatory reaction is important because a lasting proinflammatory reaction delays the healing process[11,12]. In particular, prolonged elevation of proinflammatory IL-1α, IL-6, and TNF-α can promote osteoclast function and differentiation and can subsequently hinder bone regeneration[13,26]. These processes may impact osteointegration of the new prosthesis. Of note, analysis of the individual patients revealed increasing expression of IL-6, IL-10, and IL-12 in a few patients, and such patients may be at increased risk for prosthesis failure. Studies on bone regeneration have demonstrated that harnessing and modulating inflammation can improve fracture-healing[10]. Besides antimicrobial treatment, patients affected by PJI may benefit from a localized anti-inflammatory approach.

Currently, TKA reimplantation is performed at least 6 weeks after explantation surgery in patients with no clinical signs of persisting infection and falling infectious parameters

(i.e., C-reactive protein [CRP] and white blood-cell count). Our data suggest that these commonly used parameters are not adequate to determine sufficient recovery of the bone metabolism to normal physiological levels. Orthopaedic surgeons treating PJI should consider prolonged inflammation of the surrounding bone stock potentially leading to non-optimal prosthesis osteointegration. However, it remains unknown if extension of the time between surgical procedures can improve the regenerative capabilities of bone. Future research is needed to investigate the impact on bone metabolism in detail, as a deeper understanding of the pathomechanisms is needed to illuminate novel therapeutic approaches for affected patients.

The limitations of the current study include the heterogeneity of the analyzed population, the small sample size, and differences in the involved microbial pathogens. Additionally, a potential presence of low-level inflammation in our control group of patients with osteoarthritis, as previously reported[27], may result in underestimation of the actual inflammatory levels in patients with PJI at both explantation and reimplantation.

The present study demonstrated a strong and lasting upregulation of the proinflammatory environment in the joint-surrounding osseous scaffold in patients with PJI. However, there remains a paucity of knowledge regarding the inflammation-dependent alterations in bone metabolism in PJI leading to elevated prosthesis failure rates after revision surgery. Our data suggest that modulating the inflammatory environment has potential to improve the clinical outcome in affected patients. ■

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