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The Role of Receptor Activator of Nuclear Factor-κB Ligand/Osteoprotegerin Ratio in Synovial Fluid as a Potential Marker for Periprosthetic Osteolysis Following Total Ankle Arthroplasty

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Background: Periprosthetic osteolysis is a prevalent complication following total ankle arthroplasty (TAA), implicating various cytokines in osteoclastogenesis as pivotal in this process. This study aimed to evaluate the relationship between osteolysis and the concentrations of osteoclastogenesis-related cytokines in synovial fluid and investigate its clinical value following TAA.

Methods: Synovial fluid samples from 23 ankles that underwent revision surgery for osteolysis following TAA were analyzed as the osteolysis group. As a control group, we included synovial fluid samples obtained from 23 ankles during primary TAA for osteoarthritis. The receptor activator of nuclear factor-κB ligand (RANKL)/osteoprotegerin (OPG) ratio in these samples was quantified using sandwich enzyme-linked immunosorbent assay techniques, and a bead-based multiplex immunoassay facilitated the detection of specific osteoclastogenesis-related cytokines.

Results: RANKL levels averaged 487.9 pg/mL in 14 of 23 patients in the osteolysis group, with no detection in the control group's synovial fluid. Conversely, a significant reduction in OPG levels was observed in the osteolysis group (p = 0.002), resulting in a markedly higher mean RANKL/OPG ratio (0.23) relative to controls (p = 0.020). Moreover, the osteolysis group had increased concentrations of various osteoclastogenesis-related cytokines (tumor necrosis factor-α, interleukin [IL]-1β, IL-6, IL-8, IP-10, and monocyte chemotactic protein-1) in the synovial fluid relative to the control group.

Conclusions: Our results demonstrated that periprosthetic osteolysis was associated with osteoclastogenesis activation through an elevated RANKL/OPG ratio following TAA. We assume that RANKL and other osteoclastogenesis-related cytokines in the synovial fluid have clinical value as a potential marker for the development and progression of osteolysis following TAA.

Keywords: *Total ankle arthroplasty, Osteolysis, Synovial fluid, RANK ligand, Osteoprotegerin*

Total ankle arthroplasty (TAA) has become the treatment of choice for end-stage ankle arthritis, with satisfactory long-term outcomes.[1-6] However, with complication rates as high as 30%, periprosthetic osteolysis emerges as a significant factor affecting prosthesis longevity.[1,5,7,8] The prevention, diagnosis, and management of osteolysis continue to pose considerable challenges.[9,10]

The pathogenesis of osteolysis is multifactorial.[11-13] Historically, it was attributed to debris from polyethylene wear at the articulating surfaces of implants.[14,15]

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Contemporary research, however, implicates additional factors, such as implant micromotion and chronic inflammation in response to necrotic tissue.[11,12] Despite these diverse etiologic factors, the osteoclastogenesis pathway is increasingly acknowledged as central to the osteolytic process.[11,13,16] Macrophages, monocytes, lymphocytes, and fibroblasts (in tissues around osteolytic lesions) secrete numerous cytokines that promote bone resorption and inhibit bone formation.[13,17,18] The receptor activator of nuclear factor-κB ligand (RANKL) binds to RANK receptors on osteoclast precursor cells, upregulates osteoclast differentiation, and stimulates the production of pro-inflammatory cytokines.[18]

While many studies have focused on cytokine levels and their effects in patients undergoing total hip and knee arthroplasty, the findings have yet to yield consistent conclusions.[19-25] Regarding TAA, there is a notable scarcity of data concerning the release of inflammatory cytokines in the synovial fluid of patients with osteolysis. This study aimed to explore the association between the concentration of osteoclastogenesis-related cytokines in synovial fluid and periprosthetic osteolysis following TAA, as well as to assess the clinical relevance of these cytokines.

METHODS

This study received approval from the Institutional Review Board of Chonnam National University Hospital (IRB No. CNUH-2022-405), and all participants provided written informed consent.

Patients

From January 2005 through December 2021, 40 synovial fluid samples from ankle joints were collected from patients undergoing revision TAA due to osteolysis that followed primary TAA. Primary TAA was performed using mobile-bearing HINTEGRA prostheses (Integra Lifesciences) in all cases. These samples were subsequently analyzed. The criterion for revision was progressive osteolysis, characterized by an enlargement greater than 5 mm, potentially leading to prosthesis loosening or subsidence. Progression of osteolysis was identified by comparing radiographs and computed tomography images, noting an increase in either coronal or sagittal diameter by more than 5 mm from previous images.[9] We excluded patients with rheumatoid arthritis, gouty arthritis, or a history of ankle joint infection, as well as those treated with pharmacological agents, such as bisphosphonates and denosumab, which could influence osteoclast activity and inflammatory cytokine levels. Ultimately, 23 patients (23 ankles) with osteolysis were selected as the study group (osteolysis group). For the control group, 23 patients (23 ankles) diagnosed with ankle osteoarthritis, matched for age, sex, and body mass index (BMI), were chosen. Propensity score matching was conducted to mitigate baseline characteristic disparities between the groups, considering variables like age, sex, BMI, smoking status, osteolysis location, and preoperative diagnosis. Statistical analysis confirmed a lack of significant differences in the sex distribution, mean age, or mean BMI between the 2 groups.

Collection of Synovial Fluid

Primary or revision TAA was conducted under general anesthesia using a standard longitudinal anterior approach between the tibialis anterior and extensor hallucis longus tendons for all patients. Upon incision of the anterior joint capsule, synovial fluid was aspirated from the ankle joint space using a syringe. This fluid was then centrifuged at 5,000 rpm for 20 minutes at 4 °C to remove cellular components and preserved at −80 °C until the time of assay. The samples were analyzed to measure concentrations of RANKL, osteoprotegerin (OPG), tumor necrosis factor-α (TNF-α), monocyte chemotactic protein-1 (MCP-1), interferon gamma-induced protein 10 (IP-10), and various interleukins (IL-1β, IL-6, and IL-8) and receptors.

Measurement of RANKL and OPG Levels in Synovial Fluid

The concentrations of RANKL and OPG in synovial fluid were quantified using high-sensitivity enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems). The samples were processed either undiluted or diluted, with the results reported in pg/mL. Upon completion of the assay, a stop solution was added to the ELISA plates, inducing a color transition from blue to yellow. The optical density was immediately measured using a microplate reader set to a 450-nm wavelength. To establish a standard curve, the mean optical density for each standard was plotted on the y-axis against its corresponding concentration on the x-axis, using 4-parameter logistic curve-fitting software. The formula from each standard curve was employed to calculate the specific concentrations of the analytes.

Measurement of Other Cytokine Levels in Synovial Fluid

The levels of TNF-α, MCP-1, IP-10, IL-1β, IL-6, and IL-8 were assessed in the synovial fluid. These analyses were conducted using commercially available bead-based multiplex immunoassays (MilliPlex 42-Plex Kit), processed on a Bio-Plex 200 system with high-throughput fluidics

(Bio-Rad Laboratories), and using the samples as-is. Data collection was performed using the Bio-Rad Bio-Plex suspension array system and analyzed with Bio-Plex Manager 6.0 software. The fluorescence intensity of the background was deducted from the values for each sample, standard, or control for each specific bead type. Standard curves for the assay were generated using the standards included in the Milliplex kits, and data analysis was done using 5-parameter logistic regression within the limits of detection. All assays were carried out in duplicate as per the manufacturer's instructions.

Statistical Analyses

Descriptive statistics were computed using standard methods. The Kolmogorov-Smirnov test was applied to assess the normality of the data distribution. Differences between groups in normally distributed continuous data were analyzed using the independent *t*-test. For dichotomous variables, differences were examined using either the chi-square test or Fisher's exact test. Analyses were conducted using GraphPad Prism (GraphPad Software Inc.). Statistical evaluations were reviewed by a statistician, with *p*-values less than 0.05 considered indicative of statistical significance.

RESULTS

Patient Demographics

The osteolysis group comprised 23 patients (23 ankles), matched with a control group of 23 patients (23 ankles) with primary osteoarthritis. Synovial fluid was collected at a mean of 28.8 months following primary TAA in the osteolysis group. The mean age at the time of fluid collection was 68.0 ± 4.6 years for the osteolysis group and 70.5 ± 7.3 years for the control group (Table 1). Osteolysis was observed in both the tibia and talus in 12 of 23 patients, exclusively in the talus in 8 patients and solely in the tibia in the remaining 3 patients.

Table 1. Patient Demographic Characteristics

Variable	Osteolysis group	Control group	*p*-value*
No. of patients	23	23	-
Age (yr)	68.0 ± 4.6 (59–76)	70.5 ± 7.3 (55–81)	0.239
Sex			0.238
Male	10 (43.5)	14 (60.9)	
Female	13 (56.5)	9 (39.1)	
BMI (kg/m^2)	25.5 ± 2.9 (19.8–31.8)	26.0 ± 2.5 (22.0–31.8)	0.479
DM	6 (26.1)	10 (43.5)	0.216
Current smoker	3 (13.0)	4 (17.4)	0.999
Location of osteolysis			-
Tibia	3 (13.0)	-	
Talus	8 (34.8)	-	
Tibia and talus	12 (52.2)	-	
Preoperative diagnosis			0.451
Primary osteoarthritis	14 (60.9)	13 (56.5)	
Posttraumatic osteoarthritis			
Post-ankle fracture	3 (13.0)	1 (4.4)	
Recurrent sprain	6 (26.1)	9 (39.1)	

Values are presented as mean ± standard deviation (range) or number (%).
BMI: body mass index, DM: diabetes mellitus.
*The independent *t*-test was used to analyze differences in age, BMI, and follow-up duration. The chi-square or Fisher's exact test was used to analyze differences in sex, DM, current smoker, and preoperative diagnosis. A $p < 0.05$ was considered statistically significant.

Within the osteolysis group, 16 patients (69.6%) received bone grafting and polyethylene inlay exchange. The remaining 7 patients (30.4%) underwent surgical interventions, with 1 patient receiving a talar component revision TAA and 6 patients undergoing conversion to tibiotalocalcaneal arthrodesis at the time of synovial fluid collection.

Levels of RANKL and OPG

RANKL was detected in the synovial fluid of 14 patients from the osteolysis group, whereas none of the patients in the control group had any detectable level of RANKL. The mean RANKL concentration in the osteolysis group was 487.9 pg/mL (range, 0.0–3,031.1 pg/mL), which was significantly higher than that of the control group ($p = 0.008$) (Fig. 1A).

There was evidence of OPG in the synovial fluid of all patients from both the osteolysis and control groups. The mean concentration in the osteolysis group was 3,403.6 pg/mL (range, 855.7–6,379.9 pg/mL), compared with 7,696.3 pg/mL (range, 1,857.3–17,778.7 pg/mL) in the control group (Table 2). The osteolysis group had significantly lower levels of OPG than the control group ($p = 0.002$) (Fig. 1B). Furthermore, the mean RANKL/OPG ratio of the osteolysis group (0.23) was significantly higher than that of the control group ($p = 0.020$) (Fig. 1C).

Levels of Other Inflammatory Cytokines

All patients in both the osteolysis and control groups exhibited detectable levels of the cytokines TNF-α, IL-1β, IL-6, IL-8, IP-10, and MCP-1, which are associated with bone

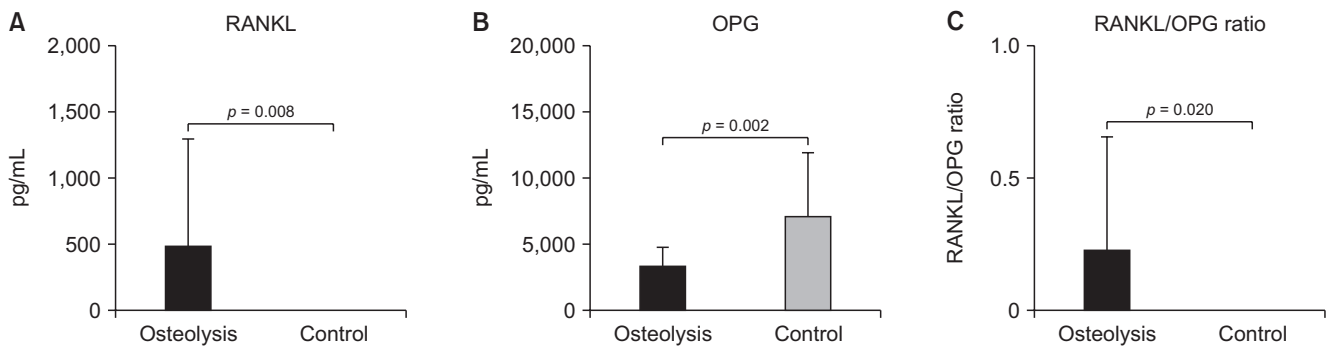

Fig. 1. Graphs showing the mean concentration of receptor activator of nuclear factor- κB ligand (RANKL; A), osteoprotegerin (OPG; B), and the mean RANKL/OPG ratio (C) in the synovial fluid of the osteolysis group and the control group following total ankle arthroplasty.

Table 2. Comparison of Levels of Osteoclastogenesis-Related Cytokines between the Osteolysis Group and Control Group Following Total Ankle Arthroplasty

Variable	Osteolysis group (n = 23)		Control group (n = 23)		*p*-value*
	Mean ± SD (range)	95% CI	Mean ± SD (range)	95% CI	
RANKL (pg/mL)	487.9 ± 786.9 (0.0–3,031.1)	166.3–809.5	-	-	0.008
OPG (pg/mL)	3,403.6 ± 1,341.1 (855.7–6,379.9)	2,855.5–3,951.7	7,696.6 ± 4,797.8 (1,857.3–17,778.7)	5,735.8–9,657.4	0.002
RANKL/OPG ratio	0.23 ± 0.42 (0.00–1.47)	0.1–0.4	-	-	0.020
TNF-α (pg/mL)	104.2 ± 59.7 (38–348)	96.2–145	48.0 ± 26.2 (10–127)	37.3–58.7	< 0.001
IL-1β (pg/mL)	65.9 ± 142.6 (18–688)	7.6–124.2	23.9 ± 5.6 (13–37)	21.6–26.2	0.118
IL-6 (pg/mL)	3,151.4 ± 4,414.3 (74–17,999)	1,347.3–4,955.5	720.5 ± 1,645.7 (12–8738)	47.9–1,393.1	0.006
IL-8 (pg/mL)	12,367.5 ± 7,791 (2,040–26,612)	9,183.4–15,551.6	2,616.2 ± 3,135.1 (15–10,447)	1,334.9–3,897.5	< 0.001
IP-10 (pg/mL)	6,623.2 ± 5,172.3 (1,824–24,238)	4,509.3–8,737.1	2,512.4 ± 1,583.5 (65–6,692)	1,865.2–3,159.6	< 0.001
MCP-1 (pg/mL)	22,890.3 ± 5,807.4 (11,710–26,672)	20,516.9–25,263.7	11,549.5 ± 8,067.5 (11–26180)	8,252.4–14,846.6	< 0.001

SD: standard deviation, CI: confidence interval, RANKL: receptor activator of nuclear factors κB ligand, OPG: osteoprotegerin, TNF-α: tumor necrosis factor α, IL: interleukin, IP-10: interferon gamma-induced protein 10, MCP-1: monocyte chemoattractant protein 1.
*The independent *t*-test was used to analyze differences in all variables, and $p < 0.05$ was considered statistically significant.

resorption (Table 2). Compared with the control group, the osteolysis group had significantly higher levels of each cytokine ($p < 0.05$) except for IL-1β (Fig. 2). Although IL-1β levels were higher in the osteolysis group, the intergroup difference was not statistically significant.

Levels of RANKL and OPG among Patients with and without Loosening

Of the 23 patients in the osteolysis group, 16 displayed stable implant fixation, while 7 exhibited implant loosening during intraoperative examination at revision surgery. In patients without implant loosening, RANKL was detected in 10 patients, with a mean level of 377.6 pg/mL. The mean level of OPG was 3,613.7 pg/mL, and the mean RANKL/OPG ratio was 0.17 (Fig. 3). In patients with implant loosening, RANKL was present in 3 out of 7 patients, with a mean level of 739.9 pg/mL. The mean OPG level was 2,923.4 pg/mL, with a mean RANKL/OPG ratio of 0.35. Although patients with implant loosening exhibited higher RANKL levels and lower OPG levels compared

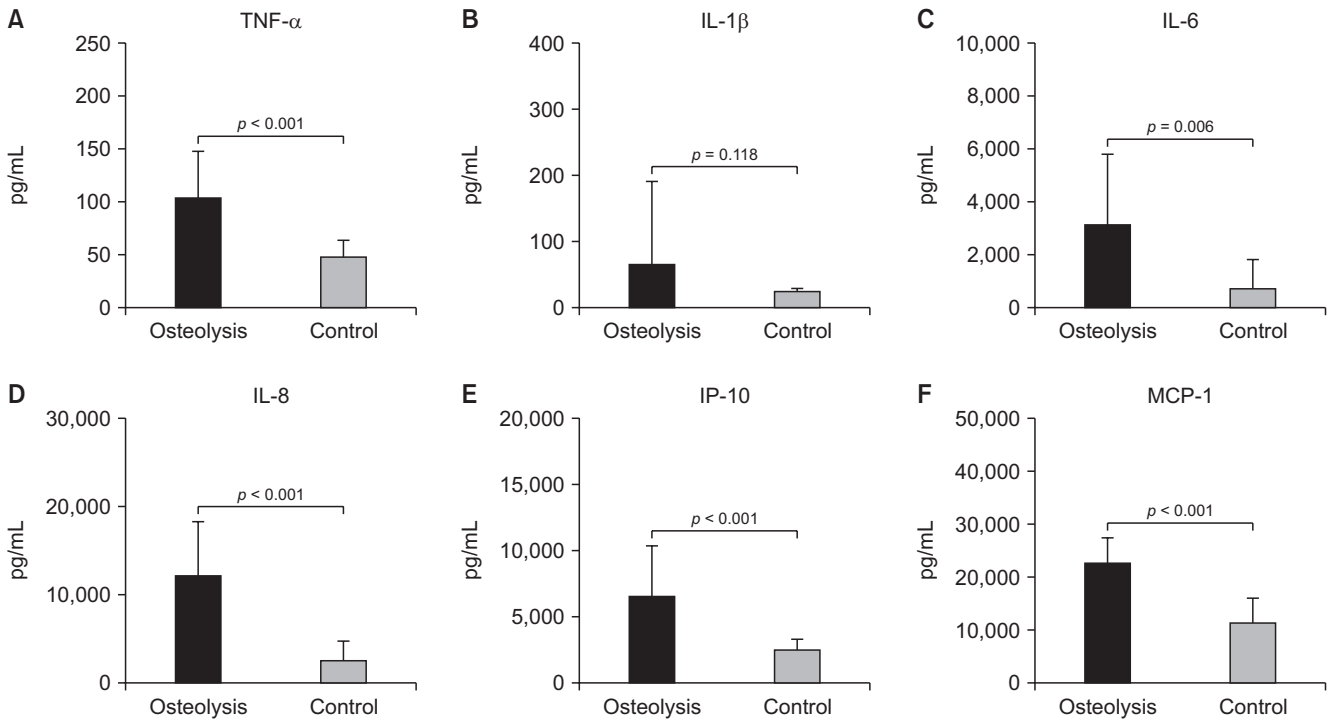

Fig. 2. Graphs showing the mean concentrations of tumor necrosis factor α (TNF-α) (A), interleukin (IL)-1β (B), IL-6 (C), IL-8 (D), interferon gamma-induced protein-10 (IP-10; E), and monocyte chemotactic protein-1 (MCP-1; F) in the synovial fluid of the osteolysis group and the control group following total ankle arthroplasty.

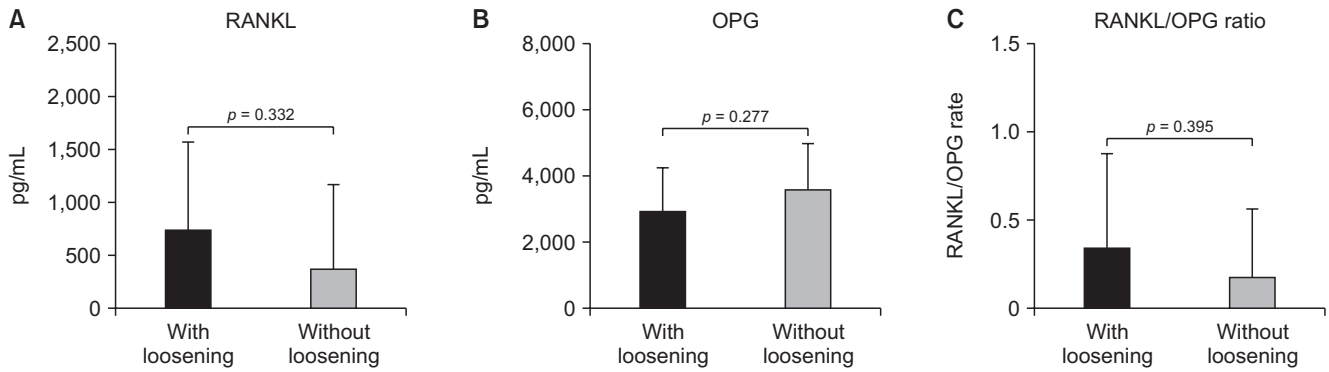

Fig. 3. Graphs showing the mean concentrations of receptor activator of nuclear factor- κB ligand (RANKL; A), osteoprotegerin (OPG; B), and the mean RANKL/OPG ratio (C) in the synovial fluid of osteolysis patients with and without implant loosening following total ankle arthroplasty.

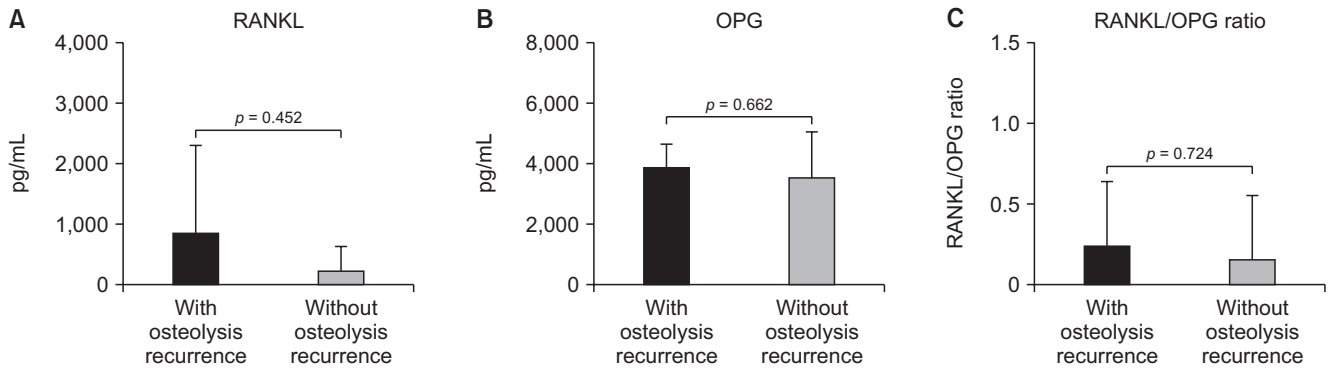

Fig. 4. Graphs showing the mean concentrations of receptor activator of nuclear factor- κB ligand (RANKL; A), osteoprotegerin (OPG; B), and the mean RANKL/OPG ratio (C) in the synovial fluid of osteolysis patients with and without recurrence of osteolysis following bone grafting.

with those without loosening, these differences were not statistically significant (p = 0.332 and p = 0.277, respectively).

Levels of RANKL and OPG in Patients with and without Osteolysis Recurrence Following Bone Grafting

With the 16 patients without loosening categorized based on osteolysis recurrence post-bone grafting, the mean RANKL levels were 852.5 pg/mL in the 4 patients with recurrence and 438.7 pg/mL in the 12 patients without recurrence (p = 0.452) (Fig. 4). In patients with recurrence, the mean OPG level was 3,887.4 pg/mL, with a mean RANKL/OPG ratio of 0.24. In patients without recurrence, the mean OPG level was 3,522.4 pg/mL and the mean RANKL/OPG ratio was 0.15 (p = 0.662 and p = 0.724, respectively).

DISCUSSION

To our knowledge, this was the first study investigating osteoclastogenesis-related cytokine levels in the synovial fluid of patients with osteolysis following TAA. A key strength of our study was the direct measurement of cytokine concentrations in synovial fluid, as opposed to serum or tissue assessments. Our findings demonstrated that the mean levels of RANKL and other cytokines, with the exception of OPG, are elevated in the synovial fluid of ankles with osteolysis relative to those with primary ankle osteoarthritis. Conversely, the mean OPG level was notably lower in the osteolysis group. These findings support the hypothesis that osteolysis is intimately associated with altered levels of cytokines within the synovial fluid.

The data revealed substantial differences in cytokine levels between the 2 groups. Initially, we noted a higher level of RANKL and a lower level of the inhibitory factor OPG in the osteolysis group relative to the control group. These findings underscore the significance of the RANKL-dependent pathway, which is recognized as a primary contributor to osteolysis. Furthermore, other cytokines, such as TNF-α, IL-1β, IL-6, IL-8, IP-10, and MCP-1, previously implicated in osteoclastogenesis in total knee and hip arthroplasty, were also found to be elevated in cases of osteolysis following TAA. This indicates that osteoclastogenesis is upregulated, and osteolysis is exacerbated by cytokine proliferation.[15] The resultant increased RANKL/OPG ratio, stemming from these cytokine alterations, is presumed to impact bone homeostasis, potentially enhancing the activity of osteoclast formation mediators.[15,22,26]

However, the precise mechanisms underlying osteolysis are obscured by the complex biological pathways and multitude of contributing factors.[13,15,18] Additionally, bone remodeling homeostasis is influenced not only by osteoclastic bone resorption but also by osteoblastic bone formation.[18] Koulouvaris et al.[27] also indicated that osteogenic activity is suppressed by the presence of wear particles, as evidenced by *in vitro* studies.

In terms of osteolysis treatment, bone grafting for the osteolytic lesions currently has been known as the only effective treatment for osteolysis without implant.[9,10,28,29] However, it does not invariably yield satisfactory results.[30] Therefore, there is a need for adjunct biological strategies to enhance bone grafting outcomes and proactively prevent osteolysis.[31] Pharmacological agents, such as denosumab and romosozumab, have the potential to modulate the inflammatory response mediators, including cytokines and their pathways, and may impede the development or progression of osteolysis if applied appropriately.[18,32] Consequently, the findings from this study could inform the development of pharmacological approaches to osteolysis following TAA.

Our study has strengths and limitations. Notably, this was the first comparative analysis of cytokines in the

synovial fluid of patients with osteolysis after TAA, offering the benefit of more accurately reflecting the local biological milieu as opposed to serum or tissue analysis. A drawback, however, was the limited quantity of samples available for analysis in patients with osteolysis. Furthermore, an ideal control group would comprise patients following TAA without osteolysis to closely match the physiological baseline of the study group. However, collecting synovial fluid from asymptomatic patients without osteolysis presents ethical and consent challenges. Another limitation was that there was noticeable variability in RANKL levels among patients with osteolysis, presumably reflective of the activity of osteolytic lesions. We did not complement our analysis with another objective tool like single photon emission computed tomography to evaluate osteolytic lesion activity. Lastly, as there are no established references for cytokine levels, including RANKL and OPG, our results should be interpreted with caution. Further research is required to establish reference values for osteoclastogenesis-related cytokines and to understand their fluctuations relative to osteolytic lesion activity.

In conclusion, this study demonstrated that osteolysis following TAA is associated with the elevation of RANKL and other osteoclastogenesis-related cytokines in the synovial fluid, along with suppression of OPG. The detection of RANKL in synovial fluid emerges as a potential biomarker for the development and progression of osteolysis. Moreover, our findings imply that osteolysis may be associated with increased osteoclast activity via an increased RANKL/OPG ratio. These insights could underpin the development of biological adjuncts for osteolysis treatment and prevention following TAA. Further validation of these results through future studies is necessary.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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