Mild aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL)-type reactions also present in patients with failed knee prostheses

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Aims

Metal particles detached from metal-on-metal hip prostheses (MoM-THA) have been shown to cause inflammation and destruction of tissues. To further explore this, we investigated the histopathology (aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL) score) and metal concentrations of the periprosthetic tissues obtained from patients who underwent revision knee arthroplasty. We also aimed to investigate whether accumulated metal debris was associated with ALVAL-type reactions in the synovium.

Methods

Periprosthetic metal concentrations in the synovia and histopathological samples were analyzed from 230 patients from our institution from October 2016 to December 2019. An ordinal regression model was calculated to investigate the effect of the accumulated metals on the histopathological reaction of the synovia.

Results

Median metal concentrations were as follows: cobalt: 0.69 μg/g (interquartile range (IQR) 0.10 to 6.10); chromium: 1.1 μg/g (IQR 0.27 to 4.10); and titanium: 1.6 μg/g (IQR 0.90 to 4.07). Moderate ALVAL scores were found in 30% (n = 39) of the revised knees. There were ten patients with an ALVAL score of 6 or more who were revised for suspected periprosthetic joint infection (PJI), aseptic loosening, or osteolysis. R2 varied between 0.269 and 0.369 for the ordinal regression models. The most important variables were model type, indication for revision, and cobalt and chromium in the ordinal regression models.

Conclusion

We found that metal particles released from the knee prosthesis can accumulate in the periprosthetic tissues. Several patients revised for suspected culture-negative PJI had features of an ALVAL reaction, which is a novel finding. Therefore, ALVAL-type reactions can also be found around knee prostheses, but they are mostly mild and less common than those found around metal-on-metal prostheses.

Article focus

- In this study, we investigated the histopathology (aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL) score) and metal concentrations (cobalt, chromium, and titanium) of periprosthetic tissues obtained from patients who underwent revision knee arthroplasty.
- We also aimed to investigate whether accumulated metal debris was associated

with ALVAL-type reactions in the synovium.

Key messages

- Almost one-third of these patients had a moderate ALVAL response. Higher ALVAL scores were mostly explained by revision indication, model type, and higher metal concentrations in the synovia.
- Compared with the concentrations found in metal-on-metal hip prostheses (MoM-THA), most of the metal concentrations were low. There were, however, a few patients with concentrations substantially higher than average.
- Several patients revised for suspected culture-negative periprosthetic joint infection (PJI) had features of an ALVAL reaction. This is a novel finding, and we suggest that an ALVAL-type metal reaction may be a reason for the chronic pain and effusion after knee arthroplasty experienced by some patients.

Strengths and limitations

- The strength of our study is the uniqueness of its data, which combine information on periprosthetic tissue metals and histopathology. In addition, clinical information is combined to assess the clinical significance of how periprosthetic tissues react to the accumulation of metal debris in primary knee arthroplasty.
- The main limitation of the present study was the small cohort size.
- Moreover, the ALVAL score has some limitations when assessing ALVAL-type reactions. Although it evaluates tissue damage and chronic inflammation, it is difficult to interpret the causes of these changes.

Introduction

The latest generation of metal-on-metal hip arthroplasty (MoM-THA) was introduced in the early 2000s. Specifically aimed at young and active patients with hip osteoarthritis, the MoM-THA was designed and marketed as a more durable alternative to the widely used metal-on-polyethylene (MoP) bearing couple.[1] However, in practice, metal particles and ions were released from the MoM-THA and accumulated in the periprosthetic soft-tissue. This led to synovial necrosis and inflammatory responses known as adverse reactions to metal debris (ARMD).[2-5] Consequently, large numbers of patients with MoM-THAs had to undergo revision surgery.[6,7] Interestingly, not only MoM-THAs have had to be revised due to ARMD, as a similar phenomenon has also been reported in MoP prostheses.[8] In contemporary knee arthroplasty, MoP is the standard bearing surface irrespective of the prosthesis design. Recently, however, interest has arisen over whether ARMD could be one aetiological factor causing unexplained pain and effusion after knee arthroplasty.[9]

ARMD is an umbrella term that describes the macroscopic and microscopic findings, such as soft-tissue necrosis, inflammation, and inflammatory masses known as a pseudotumour, seen in these patients. Aseptic lymphocyte-dominated vasculitis-associated lesions (ALVALs) describe the histological effect of lymphocytic infiltration, sometimes accompanied by a pseudotumour.[10,11]

The aetiology and pathogenesis of ARMD has been investigated extensively in relation to hip prostheses. There is, however, a paucity of evidence on how contemporary knee prostheses wear in use. In particular, evidence on the number of metal ions and particles (cobalt, chromium, and titanium) that accumulate in the periprosthetic tissues is lacking. Furthermore, it is also unclear how the periprosthetic tissues react to wear and the accumulation of metal particles in the synovium around knee prostheses. To the best of our understanding, only one previous study has investigated ALVAL scores from the periprosthetic tissues of failed knee prostheses.[12] Although attempts have been made to investigate ALVAL scores in relation to metal hypersensitivity, earlier studies have mainly investigated plasma ion concentrations without assessing histological responses.[9]

The aims of this study were to assess: 1) the histological response (ALVAL score) in the periprosthetic tissues of failed knee prostheses; 2) metal ion (cobalt, chromium, and titanium) concentrations in the periprosthetic tissue around knee prostheses; and 3) how well the metal concentrations explain the histological reaction.

Methods

Patient selection

We conducted a retrospective cohort study of 230 consecutive patients who had undergone revision knee arthroplasty at Coxa Hospital for Joint Replacement (Tampere, Finland) between 1 October 2016 and 31 December 2019. Informed consent to participate in this study was obtained from all participants. We excluded patients who had a spacer knee prosthesis and those who had undergone a planned second-stage infection revision (Figure 1).

The mean age of the patients in this study was 69 years (standard deviation (SD) 9.7), and 65% (n = 150) of the patients were women. The median time from primary operation to revision was 5.2 years (14 days to 41 years; interquartile range (IQR) 1.4 to 11). In our study, there were 47 (20%) unilateral knee arthroplasties (UKAs) and 184 total knee arthroplasties (TKAs). The most important reason for revision was instability (30%) (Table I).

Data collection

Information on each revised implant model and the dates of the primary and revision operations were collected during the revision surgeries. Other important background data were gathered from the electronic patient record system (age, sex, and indication for revision).

Sample collection

Samples from synovia were obtained during the revision operations. A total of seven samples were taken from each patient: five for bacterial cultures, one for ALVAL score measuring, and one for measurement of metal ion concentrations. Samples for bacterial cultures were taken next to implants from different sides of the joint. The other two samples were collected from the suprapatellar recess of the synovia, which allowed the best access for sufficient sample amounts. Tissue samples in all cases were taken using standard surgical instruments.

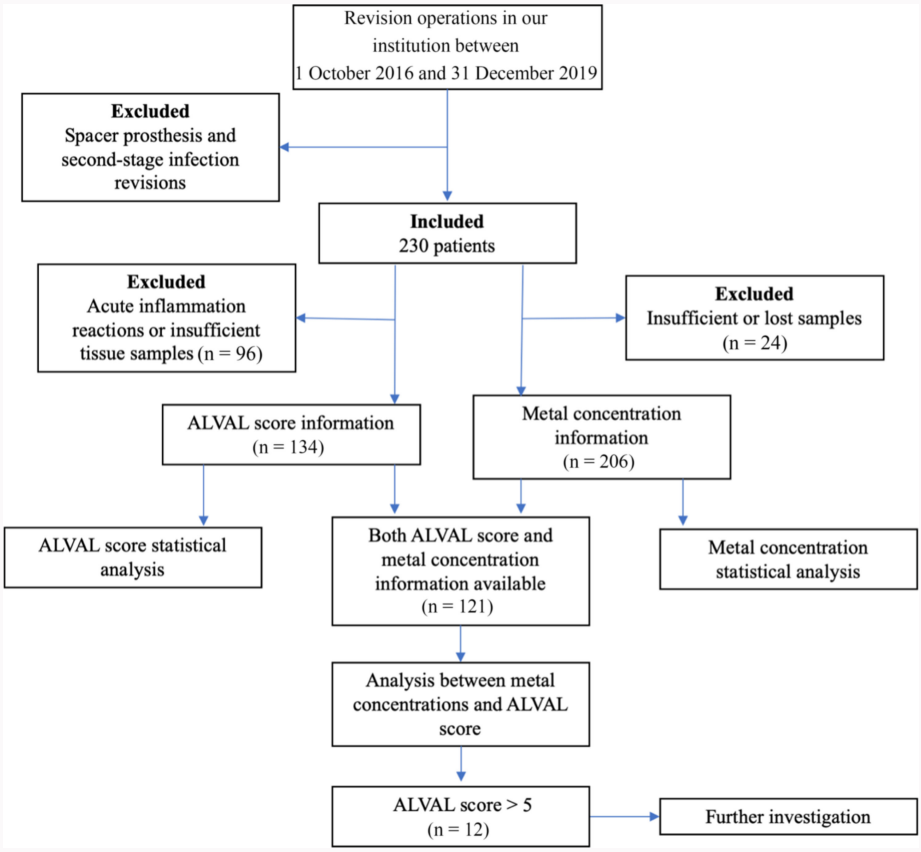

Fig. 1
Flowchart illustrating patient selection. ALVAL, aseptic lymphocyte-dominated vasculitis-associated lesions.

Metal concentration analysis

Information was collected for a total of 206 patients (90%). Subsamples (approximately 0.3 g) were obtained from the tissue samples and decomposed with 5 ml Suprapur HNO3 (Merck, Germany) with a microwave digestion technique using a CEM MDS-2000 Microwave System (CEM Corporation, USA). Then, the decomposed subsamples were diluted to 10 ml with Milli Q-water (Merck). The samples were then analyzed with an inductively coupled plasma optical emission spectrometer (ICP-OES) for aluminium, chrome, cobalt, titanium, molybdenum, and vanadium. A Thermo Electron iCAP 6600 Duo View equipped with Cetac ASX-520Hs, as well as an autosampler, were used in this study (Thermo Fisher Scientific, USA). Certified reference material NIST SRM 1576b (bovine liver) (Merck) was used to confirm the performance of the analytical procedure.

The measured metal concentrations reported were for cobalt, chromium, and titanium. We also received concentration data for aluminium, molybdenum, and vanadium. However, they were excluded from the analyses because of the inconsiderable amounts of the metals in the synovia.

ALVAL score analysis

ALVAL scores from the tissue samples were analyzed by a senior musculoskeletal pathologist (JP) in the Fimlab Oy Pathology department. The ALVAL score is a ten-point histological rank that includes the examination of synovial lining integrity (0 to 3), inflammatory cell infiltrates (0 to 4), and tissue organization (0 to 3). The synovial lining and tissue organization subscores both describe the degree of necrosis in the sample. The inflammatory cell infiltrates subscore increases when more lymphocytes are present in the sample and when there are fewer macrophages.[10]

Information on the total ALVAL score and the frequencies of each subgroup were gathered from 134 patients (58%). Those patients whose synovia samples were insufficient for analysis of the histology, and those with acute inflammation reaction, were excluded from the analysis. For further clarification of the role of higher ALVAL score, the scores of patients with an ALVAL score of 6 or more (n = 12) were reviewed from the electronic medical records. Additional demographic data were also collected, including results from pre- and intraoperative bacterial cultures, possible use of antibiotics before the samples were taken, preoperative cell count from synovial fluid, and information on possible fistula wound.

Histology figures were first scanned into digital form with Pathology Scanner (Philips, Netherlands), and then captured using Intellisite Image Management System (Philips).

Statistical analysis

Descriptive statistics were established for the whole patient cohort of 230 as counts with percentages, means with SDs, or medians with IQRs, depending on the class and distributions of each variable. Medians and IQRs of the metal concentrations were calculated for the 206 patients who had the information available. The influence of cobalt, chromium, and titanium (predictor variables) on the ALVAL score and

Table I. Descriptive statistics of the data (n = 230).

Variable	Data
Mean age, yrs (SD)	69 (9.7)
Sex, female, n (%)	150 (65)
Median time from primary operation to revision, yrs (IQR)	5.2 (1.4 to 11)
Retrieved implants, n (%)	
NexGen	64 (28)
PFC	61 (27)
Oxford	46 (20)
Triathlon	29 (13)
Vanguard	6 (3)
Other	24 (10)
Reason for revision, n (%)	
Instability	68 (30)
Periprosthetic joint infection	53 (23)
Malalignment	25 (11)
Pain and/or stiffness	24 (10)
Progression of osteoarthritis	24 (10)
Aseptic loosening	12 (5)
Polyethylene wear and/or osteolysis	12 (5)
Other	12 (5)

IQR, interquartile range; SD, standard deviation.

Table II. Aseptic lymphocyte-dominated vasculitis-associated lesions score and subscore frequencies.

ALVAL score	Grade	Data, n (%)
Total ALVAL score	Low (0 to 4)	95 (71)
	Moderate (5 to 8)	39 (29)
	High (9 to 10)	0
Synovial lining	0	11 (8.2)
	1	87 (65)
	2	27 (20)
	3	9 (6.7)
	4	0
Inflammatory infiltrate	0	8 (6.0)
	1	83 (62)
	2	41 (31)
	3	2 (1.5)
Tissue organization	0	7 (5.2)
	1	83 (62)
	2	40 (30)
	3	4 (3.0)

ALVAL, aseptic lymphocyte-dominated vasculitis-associated lesions.

subscores (outcome variables) was investigated using the ordinal regression model. Outcome variables were the ALVAL score and subscores (inflammatory infiltrates, synovial lining, and tissue organization).

Distribution of the metal concentrations was highly skewed. Therefore, they were transformed into a logarithmic scale for computing the ordinal regression model. After transformation, the distribution was observed to be normal from the histogram. The ordinal regression model was adjusted for age, sex, reason for revision (consisting of four groups: instability, malalignment, periprosthetic joint infection (PJI), and other), and implant design (consisting of four groups: PFC (DePuy Synthes, USA), NexGen (Zimmer Biomet, USA), Oxford (Zimmer Biomet), and other). Ordinal regression models were calculated using the interaction of all three metals as a predictor and applied to all outcome variables. R^2 values were investigated from each model and arranged into a table. The relative importance figure was printed from all the models. Statistical analyses were performed using R 4.0.2 (R Foundation for Statistical Computing, Austria), with the packages tidyverse, dplyr, ggfortify, and rms.

Results

In total, 134 patients had their ALVAL score examined (Table II). In 30% (n = 39) of these patients, a moderate ALVAL reaction was evident in the synovial samples. Overall, 12 (9%) patients had an ALVAL score of 6 or more. Five of these patients underwent a revision operation due to suspected chronic PJI, but only two had positive bacterial culture preoperatively. Further, all the multiple bacterial cultures (minimum of five) obtained from these patients during revision surgeries remained negative. All ten of these patients had a moderate histological ALVAL-type reaction (Table III). The histology between these samples varied. There were plasma cell reactions, also accompanied by perivascular lymphocytic aggregates. In addition, epithelial necrosis with fibrin formation and macrophages were detected (Figure 2).

The median metal concentrations varied between 0.69 μg/g and 1.6 μg/g (Table IV). Titanium had the highest median concentration, but cobalt had a higher absolute range and IQR.

In ordinal regression analysis, R^2 for total ALVAL score was 0.278, and the relative importance between the variables was most apparent with model type, indication for revision, cobalt and chromium and their interaction term (logCo * logCr * logTi) (Table V, Figure 3, Supplementary Figures a to d). In subscore analysis, R^2 varied between 0.269 and 0.369 (Table V). The most important variables for the subscores were model type, indication for revision, interaction with chromium and cobalt, and age (Figure 3).

Discussion

In the present study, we investigated the relationship between periprosthetic metal concentrations and ALVAL score in patients with failed knee prostheses. We established that almost one-third of these patients had a moderate ALVAL response. Higher ALVAL scores were mostly explained by revision indication, model type, and higher metal concentrations in the synovia. Compared with the

Table III. Overview of the patients with aseptic lymphocyte-dominated vasculitis-associated lesions score of 6 or more.

Patient	Age, yrs	Sex	Time from primary, yrs	Indication for revision	Cell count (× 10 E6/l)	Fistula	Antibiotics preoperatively	Preoperative bacterial culture	Intraoperative bacterial culture	ALVAL score	Inflammatory infiltrates	Synovial chromium	Synovial cobalt
1	64	F	3.9	Chronic infection	5,650	No	No	Neg	Neg	8	3	5.6	7.2
2	83	F	6.0	Chronic infection	24,000	Postop	Yes	*Staph lugdunensis*	Neg	7	2	0.1	0.1
3	89	M	17.0	Chronic infection	19,533	No	Yes	*Staph spp.*	Neg	7	2	9.0	43.6
4	82	F	7.1	Chronic infection	15,000	No	Yes	Neg	Neg	8	2	0.40	0.11
5	69	M	1.3	Chronic infection	22,600	No	No	Neg	Neg	6	2	0.04	0.01
6	76	F	14.3	Progression of OA	Not done	No	No	Neg	Neg	7	2	2.9	172
7	69	F	5.1	Aseptic loosening, pain	1,300	No	No	Neg	Neg	7	2	3.3	3.2
8	78	F	5.7	Aseptic loosening	2,170	No	No	Neg	Neg	7	2	0.5	0.4
9	79	M	3.6	Aseptic loosening, pain	7,267	No	No	Neg	Neg	7	2	13.6	11
10	75	M	16.1	Aseptic loosening	1,510	No	No	Neg	Neg	6	3	4.1	4.5

ALVAL, aseptic lymphocyte-dominated vasculitis-associated lesions; F, female; M, male; neg, negative; OA, osteoarthritis; postop, postoperative; *Staph*, *Staphylococcus*; *Staph lugdunensis*, *Staphylococcus lugdunensis*.

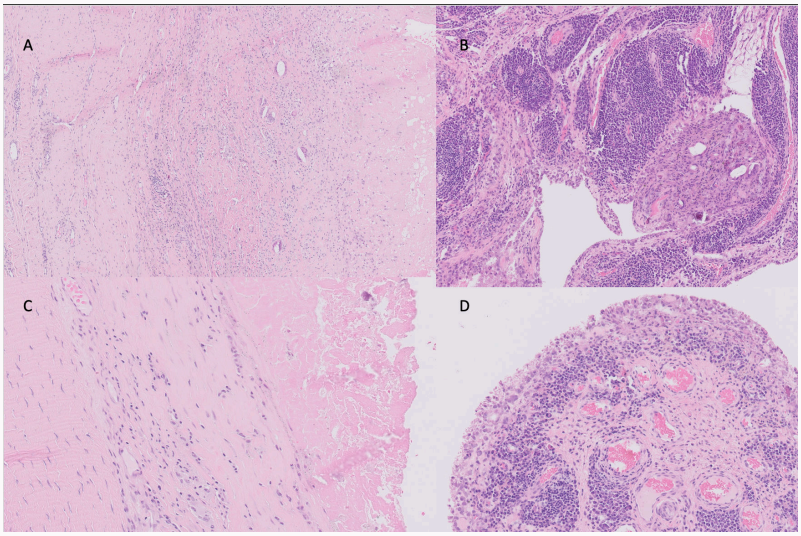

Fig. 2
Synovial tissue histology. a) Foreign body reaction with epithelial necrosis and macrophages. b) Chronic inflammation with perivascular plasma cells. c) Epithelial necrosis and fibrosis formation. d) Perivascular plasma cells and lymphocytes. All images were first scanned with Pathology Scanner SG300 (Philips, Netherlands), and then images were captured with Intellisite Image Management System (Philips).

concentrations found in MoM-THA, most of the metal concentrations were low. There were, however, a few patients with concentrations markedly higher than average.

Kurmis et al[12] reported a high correlation between ALVAL score and poor patient-reported functional outcome in patients with failed primary TKAs. In their study, however, a different mechanism was used to evaluate ALVAL reactions, as they did not use the original definition of ALVAL score by Campbell et al.[10] Arnholt et al[13] investigated the association between periprosthetic tissue metal concentrations, sample

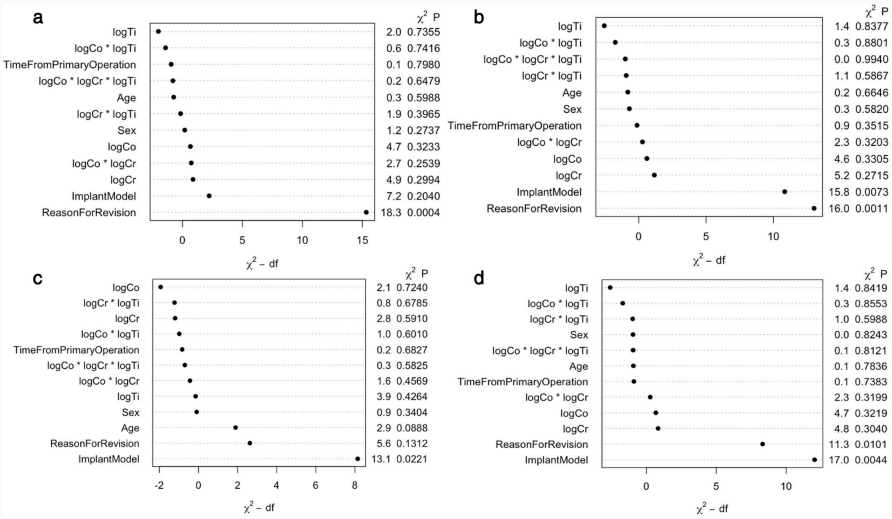

Fig. 3
Relative importance of the ordinal regression model logCo * logCr * logTi to: a) total aseptic lymphocyte-dominated vasculitis-associated lesions score; and b) to d) subgroups (B - synovial lining, C - inflammatory infiltrates, D - tissue organization).

Table IV. Synovial metal concentrations (n = 206).

Metal	Median, µg/g	IQR, µg/g	Range, µg/g
Cobalt	0.69	0.10 to 6.10	0 to 1,140
Chromium	1.08	0.27 to 4.10	0.02 to 620
Titanium	1.63	0.90 to 4.07	0.10 to 199

IQR, interquartile range.

Table V. Ordinal regression model investigating logCo * logCr * logTi effect on total aseptic lymphocyte-dominated vasculitis-associated lesions score and subgroups: R^2 values.

Variable	R^2
ALVAL score	0.278
Inflammatory infiltrates	0.269
Synovial lining	0.357
Tissue organization	0.369

ALVAL, aseptic lymphocyte-dominated vasculitis-associated lesions.

location, and inflammatory cytokines in necropsy retrieved from TKAs. They found elevated cobalt, chromium, and titanium concentrations in the periprosthetic tissues. However, the elevated concentrations were not associated with inflammatory cytokines. In the study by Arnholt et al,[13] the highest detected metal concentration medians were cobalt followed by chromium and titan. After conversion into a similar quantity as our measurements (µg/g), these corresponded to approximately thousandths of our concentrations.[13]

Lehtovirta et al[14] reported the highest medians of metal concentrations (µg/g) in MoM-THAs with chromium concentrations of 39.2 (range: 0.4 to 1,955) followed by cobalt and titanium. In their study, metal concentrations were investigated using the same method as our study. Interestingly, there were a few patients in our data with abnormally high metal concentrations around the knee prostheses that were similar to the concentrations observed around MoM-THAs. The medians of the metal concentrations were, however, small when compared to those observed in MoM-THAs. We can conclude, therefore, that metal particles are also released from knee prostheses, although in much smaller quantities.

ARMD is an umbrella term describing the macroscopic and microscopic findings in the periprosthetic tissues caused by metal debris. ARMD was originally reported in patients with MoM-THAs. Under this umbrella term, the following manifestations were reported: soft-tissue necrosis, inflammation, and inflammatory masses known as pseudotumours.[3] It is likely that ARMD is not the result of a single cascade of molecular events. Indeed, several different pathogenetic mechanisms have been proposed such as foreign-body metal reaction with a high number of macrophages, direct cytotoxic reaction causing necrosis, immunological ALVAL, and wear-related ALVAL-type reactions.[3-5,10] In ALVAL, lymphocytic infiltration and necrosis are seen histologically and are sometimes accompanied by a pseudotumour.[11] Type IV hypersensitivity response to metal debris has also been suggested as a cause.[10] However, ALVAL-type responses may also result from the accumulation of excess metal debris.[5] According to the results of the present study, there is also an ALVAL reaction seen around knee prostheses, although this response is not as strong as that seen around MoM-THAs. Among the 134 knees analyzed in this study, one patient was reported with pseudotumour-like masses detected in revision surgery. The histology around the knee prosthesis can, therefore, be one aetiological factor to explain the unclear pain in patients with knee prostheses.

In the present study, moderate-to-high ALVAL scores (5 to 8) were also surprisingly common (prevalence of 30%, n = 39). Indeed, there were 12 patients with an ALVAL score of 6 or more. Of these, we found that two patients had an obvious

acute PJI. The remaining ten patients had undergone revisions due to suspected PJI, aseptic loosening, or osteolysis. Only two patients had positive synovial fluid bacterial culture preoperatively, and all the bacterial cultures obtained perioperatively during knee revision surgery remained negative. Furthermore, all these patients had histology that was in line with chronic inflammatory reaction that indicated features of an ALVAL-type reaction. This included more lymphocytic-type inflammatory reactions and epithelial necrosis. One patient also had pseudotumour-like masses detected in revision surgery. This is a novel finding that may indicate that some of the patients currently diagnosed with chronic PJI (culture-negative) may be suffering from an ALVAL-type periprosthetic inflammation. Moreover, experience from MoM-THAs gives some support to this finding, as it has been shown that differential diagnostics between PJI and ARMD may be very difficult as the clinical manifestations might be very similar.[14–16] Further research and confirmatory findings from other studies are therefore needed to further clarify this issue.

The concentrations of metals in the synovia sufficiently explained higher ALVAL scores in the regression model measured by R^2. In the analysis of the relative importance of different variables, certain implant designs were the most important variable, whereas the different metals used were the second-most important variable.

This study has some limitations that must be considered. The main limitation of the present study was the small cohort size. Although 121 patients had all the required data (ALVAL and metal concentrations), only a few patients had a suspected ALVAL-type reaction. Therefore, the statistical power to detect associations is limited. Secondly, the assessment of ALVAL-type reactions using the ALVAL score has some limitations. Although the ALVAL score evaluates tissue damage and chronic inflammation, it is extremely difficult to interpret the causes of these changes.

The strength of our study is the uniqueness of its data, which combine information on periprosthetic tissue metals and histopathology. In addition, clinical information is combined to assess the clinical significance of how periprosthetic tissues react to the accumulation of metal debris in primary knee arthroplasty. Although this topic has been studied a great deal in THA, to date, only one previous study has been conducted on ALVAL scores in knee arthroplasty. Furthermore, in our study, we measured the metal concentrations using the exact same method used in a previous study on revised MoM-THAs.[13]

In conclusion, to our knowledge this is the first study to investigate the concentrations of metals in the periprosthetic tissues and their effect on the histopathology after primary knee arthroplasty. We found that metal particles can be released from the knee prosthesis and accumulate in the periprosthetic tissues to variable degrees. We also observed ALVAL-type reactions in the periprosthetic tissues of failed knee prostheses. However, most of these reactions were moderate and seem to be less common than in MoM-THAs. Higher ALVAL score was associated with higher metal concentrations and knee prosthesis design. Interestingly, several patients revised for suspected culture-negative PJI had features of an ALVAL-type reaction. This is a novel finding, and we suggest that an ALVAL-type metal reaction may be a reason for the chronic pain and effusion after knee arthroplasty experienced by some patients.

Supplementary material

Multivariable ordinal regression models.

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A. Reito: Conceptualization, Methology, Formal analysis, Writing – review & editing.
J. Parkkinen: Resources, Formal analysis.
S. Peräniemi: Resources.
J. Vepsäläinen: Resources.
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Data sharing

The datasets generated and analyzed in the current study are not publicly available due to data protection regulations. Access to data is limited to the researchers who have obtained permission for data processing. Further inquiries can be made to the corresponding author.

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Ethical review statement

This study was approved by the Ethical Committee of the Pirkanmaa Hospital District (R16089). Furthermore, an informed consent form was signed by all patients giving permission to obtain and analyze tissue samples.

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