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Measurement of the inflammatory response in the early postoperative period after hip and knee arthroplasty

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Abstract

Background: The aim of this study was to identify an inflammatory marker with fast and predictable kinetics to enable future discrimination between normal postoperative inflammation and potential infection after total hip and knee arthroplasty cases.
Methods: Changes in serum levels of C-reactive protein (CRP), interleukins (IL) 1β, 6 and 8 and NT-proCNP peptide were measured before and during first 5 postoperative days in 100 patients undergoing total hip or knee arthroplasty. We also compared two methods to describe the magnitude of inflammation – applying separate two sample tests at each time point, and summary measures – area under the curve (AUC).
Results: IL-6 showed a similar kinetics pattern to the CRP in response to surgical trauma. Significantly greater level changes in all markers but NT-proCNP were observed in knee patients. Persisting high levels of CRP, but not other markers, were observed in obese hip patients. IL-6 was found to be an adjunct to routine CRP use.
Conclusions: IL-6 has faster kinetics and is less influenced by patient weight, therefore it seems to be more useful in clinical practice. Summary measures describe the inflammatory response well and are easier to analyze than multiple analyses of single time points.

Keywords: arthroplasty; C-reactive protein; cytokines; immune response; interleukin-6; serial measurements.

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Introduction

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) trigger inflammatory reactions, which can be described by changes in the neuroendocrine, protein and cytokine systems [1, 2]. C-reactive protein (CRP), an acute-phase protein produced in hepatocytes and macrophages, is the most commonly used marker in clinical practice [3]. Its values increase between the second and third postoperative day and return to normal values within several weeks after surgery [4]. Various cytokines and peptides have been reported to undergo a more rapid increase and quicker return to normal values after surgery [5]. With the promise of more robust surveillance of inflammatory response, cytokine and peptide measurements would offer a clinical advantage and justify the use of more sophisticated laboratory methods.

The aim of our study was to compare three cytokines [interleukin-1β (IL-1β), IL-6 and IL-8] and a pro-peptide [N-terminal propeptide of C-type natriuretic peptide (NT-proCNP)] with CRP, in order to find a marker:

- best describing the difference in the magnitude of surgical trauma and resulting inflammatory response between THA and TKA;
- with predictable and simple kinetics and high dynamics, so it can be used during the currently short hospital stay for elective surgery, and the use of which would not require additional blood draws;
- independent from numerous patient-specific variables, such as increased body weight, a frequent comorbidity in patients undergoing total joint arthroplasty.

The choice of markers was dictated both by surveying the literature and availability of standardized tests used in our hospital.

We also tested an alternative method of analysis to describe the patient's inflammatory response with summary measures, namely the area under the curve (AUC) of the particular value over time. We hypothesized that it would be easier clinically to apply the AUC rather than comparing peak values, time to return to normal values, or multiple single time point comparisons, which we used previously.

Materials and methods

Patients

The study was conducted prospectively on 100 patients operated at the tertiary care teaching hospital. There were two groups – the TKA and THA group. The surgical technique, surgical team and postoperative care were standardized and kept uniform within each group. Patients were mobilized and a standardized rehabilitation protocol was started on the first day after surgery in both groups. All patients with inflammatory arthropathies or with anti-inflammatory treatment before surgical intervention were excluded from this study. The operations were performed under spinal anesthesia. All patients received three doses of first generation cephalosporin intravenously as the perioperative prophylaxis (first dose within 30 min of skin incision and then 8 and 16 h postoperatively). All THAs were cementless (BiContact and ScrewCup from Aesculap, Tuttlingen, Germany) and all the knees were cemented (Triathlon knee and SimplexP cement from Styker, Mahwah, NJ, USA). Postoperative analgesic protocol excluded the use of anti-inflammatory drugs.

Peripheral venous blood samples were collected 24 h before the day of operation and then every day for 5 postoperative days. To control for circadian rhythms, all samples were drawn at the same hour in the morning (7 am) and only the patients undergoing the first interventions each day were included. The samples were stored in 4 mL serum separation tubes with clot activator. The tubes were transported within an hour to the laboratory for biochemical processing. They were centrifuged at 1500×*g* for 15 min at room temperature, the serum was collected and frozen at –80 °C. The inflammatory parameter levels were determined after collection of all the sera.

This study has been carried out in accordance with the Declaration of Helsinki (2008) of the World Medical Association. The Institutional Review Board had approved this study before enrollment (no. 24/02/2010). All patients gave their written informed consent to the participation in this study prior to the enrollment. All patient were followed up for at least 2 years, in order to fulfill the periprosthetic joint infection surveillance criteria of the Centers for Disease Control and Prevention [6].

Measurements of inflammatory parameters

All of the parameters were tested in the same laboratory. The levels of CRP were established in the sera of all the participants by immunoturbidymetry, using the Turbitex CRP Ultra kit (Biocon Diagnostik, Vöhl/Marienhagen, Germany) on the Metrolab 2300 apparatus (UV-Vis Metrolab S.A., Buenos Aires, Argentina). The CRP content of each serum was tested three times and the results expressed as the mean in mg/L.

The levels of IL-1β, IL-6 and IL-8 were analyzed in the sera by the method of enzyme-linked immunosorbent assay (ELISA) using the PeliKine-compact human ELISA system (Sanquin, Amsterdam, The Netherlands). The minimum levels detectable using the ELISA kits were 0.4 pg/mL for IL-1β, 0.2 pg/mL for IL-6 and 1 pg/mL for IL-8. Intra- and inter-assay coefficients of variation were <10% for all the interleukin assays. The tests were conducted according to the manufacturer's instructions. The optical density was read using a Multiskan RC V1.5-0 450 nm microplate reader (Labsystems, Helsinki, Finland) at 450 nm. The cytokine content of each serum was tested three times and the results expressed in pg/mL are the means of these.

The levels of NT-proCNP were established in 24 patients (in the first 12 patients out of both groups) by the ELISA kits for the quantitative determination of human NT-proCNP (Biomedica, Vienna, Austria). The means were expressed in pg/mL after triple testing of each sample. Intra- and inter-assay coefficients of variation were <5% for this assay.

Statistical analysis

Patient demographics were summarized by means and standard deviations (SDs) for continuous variables. Frequencies and percentages were used for categorical and discrete variables. All laboratory values were expressed as mean±SD when the distribution was normal and symmetric, and median [with interquartile range (IQR) or range] when the distribution was right-skewed. Pre- and postoperative marker levels were compared using Wilcoxon rank sum test; Student's t-test was also used, when there was a normal distribution of means. All statistical analyses were performed using the R 3.0 software (R Foundation for Statistical Computing, Vienna, Austria). We considered probability value of <0.05 significant.

Results

Study group

A total of 100 patients participated in the study, 66 females and 34 males. They were divided into two groups. Group I included 51 patients who underwent TKA (12 men and 39 women, mean age: 68 years±8, range: 55–82). Group II included 49 patients who underwent THA (22 men and 27 women, mean age: 61 years±10, range: 25–86). There was a trend for hip patients to be younger than knee patients (Wilcoxon signed-rank test, p=0.05). Median BMI for the entire cohort was 29 kg/m^2 (range 19–40), with a tendency for higher values in the TKA group (median BMI of 31), compared to THA (median BMI of 26). All patients

completed 2-year follow-up and were infection-free at the latest appointment. We did not experience any surgical nor medical complications in the study groups. The overall transfusion rate was 4% in both groups, all of those patients received one pack of blood.

Acute phase reactants' kinetics

For the entire study population (n=100), CRP rose after the surgery. The largest increase in CRP was noted during the first postoperative day, with the highest median concentration on the second (for TKA, 120.8 mg/L, IQR 10.1) and third (for THA, 106.5 mg/L, IQR 62.8) postoperative day. The values of the peaks differed significantly (Wilcoxon rank sum test with continuity correction, p=0.02). Thereafter, the concentration decreased in a single-phase manner, without reaching normal levels (CRP <10 mg/L) within the study period (Figure 1). Significantly higher CRP values were observed on days 1, 2, 4 and 5 postoperatively in TKA group (Wilcoxon rank sum test, p<0.02 for all comparisons). The inflammatory response, measured as the AUC, was significantly higher in the total knee arthroplasty group: median of 458.2 in TKA group versus 367.5 in THA group (Wilcoxon's rank sum test with continuity correction, p=0.02).

CRP kinetics were different in patients with normal and elevated body weight. After total hip arthroplasty, patients with a greater body mass (BMI>24.9 kg/m^2) had higher median concentrations of CRP on all postoperative days, with significant differences on days 2–5 (Wilcoxon's rank sum test, all p<0.01, see Table 1). The analysis for total knee patients did not yield any significant differences (Wilcoxon's rank sum test, all p>0.05), which may due to the fact that only three of our patients undergoing TKA had normal body weight. Summary measures analysis (AUC) revealed significant differences also only in THA group, with median AUC for overweight patients of 424.9 (range, 96.2–553.4) and median AUC of 235 (range, 79.1–563.6) for patients with normal body weight (Figure 2).

The concentrations of IL-6 changed within the first 5 postoperative days. In both hip and knee patients, the maximum values were followed by a single-phase decline (Figure 3). The highest median concentrations were observed on the first day for TKA (197 pg/mL, IQR 271.2) and second postoperative day for THA (50.7 pg/mL, IQR

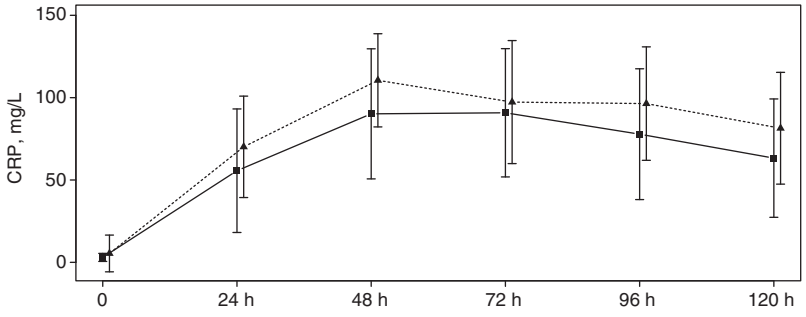

Figure 1: CRP concentration changes for THA and TKA.
Squares: THA; triangles: TKA; values are means±SD.

Table 1: Medians for all time-points for C-reactive protein in total hip arthroplasty and total knee arthroplasty groups.

Parameter	THA			TKA		
	Median value BMI<25 kg/m^2	Median value BMI>24.9 kg/m^2	p-Value	Median (mean[a]) BMI<25 kg/m^2	Median (mean[a]) BMI>24.9 kg/m^2	p-Value
No. Of patients	14	35		3	48	
CRP preop	2.3	2.5	0.92	0.6	2.6	0.41
CRP 24 h	24.8	62.7	0.09	63.7[a]	70.5[a]	0.71[a]
CRP 48 h	80.6	113.4	<0.01	106.4	120.8	0.37
CRP 72 h	62.5	114.9	<0.01	99.9	118.0	0.22
CRP 96 h	37.7	107.1	<0.01	58.1	106.0	0.31
CRP 120 h	34.1	77.1	<0.01	44.7[a]	83.7[a]	0.06[a]

[a]Comparisons were performed between overweight patients (BMI>24.9 kg/m^2) patients with normal weight (BMI<25 kg/m^2) with Wilcoxon's rank sum test. Student's t-test was used twice, when there was normal distribution of means.

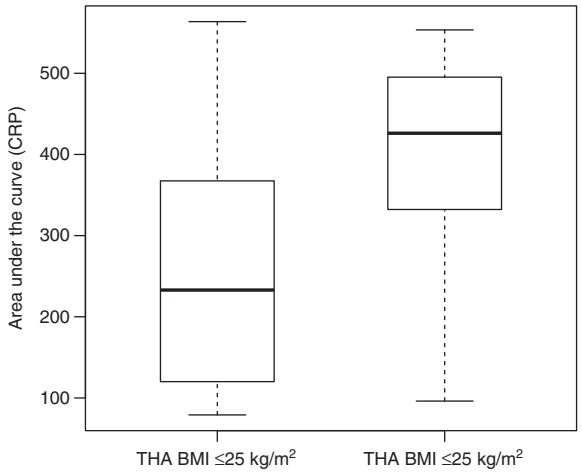

Figure 2: CRP AUC boxplots for different BMI ranges in THA patients. Values are medians (thick lines), interquartile ranges (boxes) and ranges (whiskers).

36, p<0.01). The values for IL-6 were also different for THA and TKA (Wilcoxon's rank sum test, p<0.01 for all time points; Figure 3). The same observation was made with the use of summary measures: median AUC was 147.7 for THA and 325.5 for TKA (Wilcoxon's rank sum test, p<0.01).

IL-6 kinetics did not differ between overweight and normal weight patients in both THA and TKA group for both THA and TKA, see also Table 2) and AUC analysis (two sample t-test for THA: p=0.53, Wilcoxon rank sum test for TKA: p=0.58).

The values for both IL-1β and IL-8 did not undergo major changes during the first 5 postoperative days (Figure 4). The pattern of changes seemed to be sinusoidal – concentrations were higher than every other day, starting on the day before surgery.

NT-proCNP kinetics also presented a sinusoidal pattern of changes – concentrations were higher than every other day, starting on the day before surgery (Figure 5). No difference was found between total hip and total knee cases (median AUC 5.7 in THA vs. 4.4 in TKA; Wilcoxon's rank sum test, p=0.55). The NT-proCNP measurements were discontinued after interim statistical analysis of the first 24 patients' results.

None of the patients have been diagnosed with prosthetic joint infection at 2-year follow-up. We calculated and found no statistical difference in CRP, IL-6 and NT-proCNP levels between male and female patients. There was also no correlation with other medical comorbidities or surgical time.

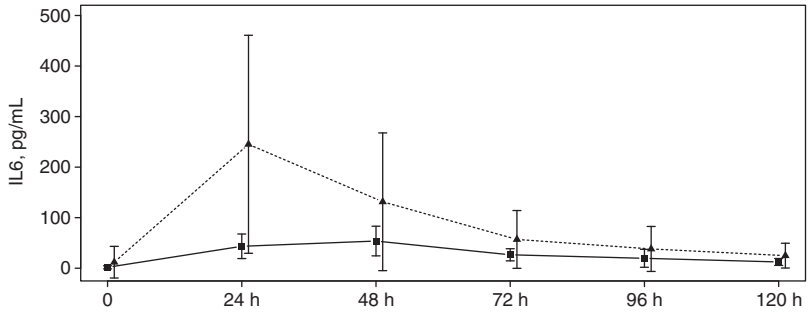

Figure 3: IL-6 means, grouped by procedure.
Squares: THA; triangles: TKA; values are means±SD.

Table 2: Medians for all time-points for interleukin-6 in total hip arthroplasty and total knee arthroplasty groups.

Parameter	THA			TKA		
	Median value BMI<25 kg/m²	Median value BMI>24.9 kg/m²	p-Value	Median value BMI<25 kg/m²	Median value BMI>24.9 kg/m²	p-Value
IL-6 preop	2.4	1.3	0.65	18.4	11.5	0.11
IL-6 24 h	36.9	48.3	0.21	275.6	243.3	0.46
IL-6 48 h	54.5	53.2	0.89	77.8	134.8	0.75
IL-6 72 h	22.6	29.6	0.05	55.4	57.1	0.92
IL-6 96 h	20.1	19.2	0.12	34.9	38.3	0.73
IL-6 120 h	11.3	13.2	0.36	26.5	24.8	0.92

Comparisons were performed between overweight patients (BMI>24.9 kg/m²) patients with normal weight (BMI<25 kg/m²) with Wilcoxon's rank sum test.

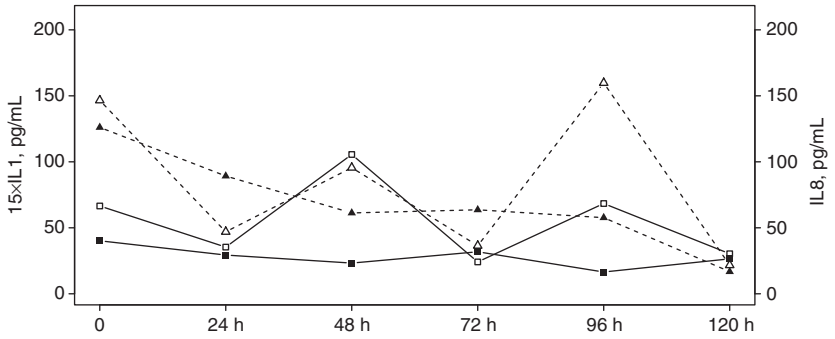

Figure 4: Changes in IL-1β and IL-8 concentrations for THA and TKA.
Note that IL-1β concentrations are ×15, to fit the curves in the same graph; Empty squares: IL-8 THA, full squares: IL-1β THA; Empty triangles: IL-8 TKA, full triangles: IL-1β TKA; values are means.

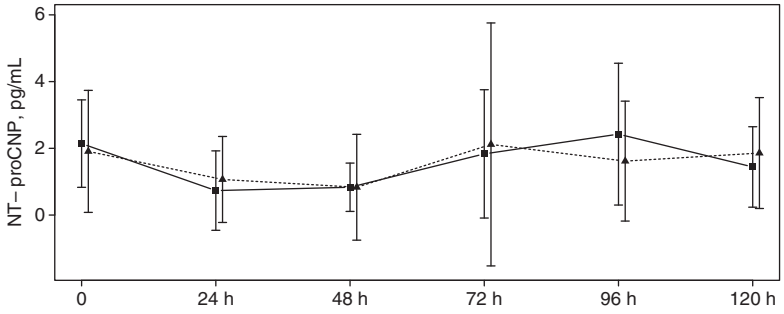

Figure 5: Mean NT-proCNP concentrations for THA and TKA.
Squares: THA, triangles: TKA; values are means±SD.

Discussion

Serum levels of CRP, IL-1β, IL-6, IL-8 and NT-proCNP were defined for 5 days postoperatively in 100 total hip and knee replacement patients. The most important finding of this study was that IL-6 showed a similar kinetics pattern to the CRP in response to surgical trauma. However, the relative concentration changes and dynamics of the process are much higher. The decrease from the peak IL-6 values occurs on the second postoperative day, compared to the third and fourth postoperative day for CRP. Other inflammatory markers either did not undergo any significant changes (IL-1β) or their level changes were not clearly associated with surgical trauma (IL-8 and NT-proCNP). Another important finding was that higher peak values and higher overall response (both multiple time-point comparisons and AUC) were observed in total knee arthroplasty patients. Finally, obesity did not influence the IL-6 response pattern and values, as it did the CRP.

There are numerous markers used to assess the inflammatory response to total joint replacement. The local response to joint replacement can be measured, but currently it is not as easily done because of decreasing use of drains, technical difficulties and increased infection risk of multiple sampling techniques [7]. Thus, much of the research is focused on peripheral inflammatory response, with serum CRP being the most studied molecule [3]. Our findings of a postoperative increase in CRP serum concentrations are consistent with previous reports [8–10]. The peak median values were observed at 72 h postoperatively for THA – 106.5 mg/L (IQR 62.8) and at 48 h for TKA – 120.8 (IQR 10.05). Peak CRP levels vary between 100 and 260 mg/L for both procedures [1, 11].

In our study, there was statistically significant difference in the inflammatory response between TKAs and THAs. This difference was evident in the CRP and IL-6 levels, but not in other markers (see Table 3 for the AUC values of CRP, interleukins and NT-proCNP).

The CRP is believed to reflect the extent of tissue damage during orthopaedic surgery [12]. Larsson et al. showed that the CRP kinetics seemed to depend on the proportion of bone and muscle damage [10]. Also, peak levels of CRP are higher after TKA, compared to THA [13]. Neumaier et al. suggested that bone marrow trauma induces most of the CRP response. The greater amounts of bone marrow reaching the lung, the higher CRP values [12].

Table 3: Median area under the curve measurements for all molecules studied.

Parameter	Total hip arthroplasty	Total knee arthroplasty	p-Value
CRP	367.5	458.2	**0.02**
IL-1b	4.6	8.1	**<0.01**
IL-6	147.7	325.5	**<0.01**
IL-8	146.7	279.5	**0.01**
NTproCNP	5.7	4.4	0.55

Comparisons between total hip arthroplasty and total knee arthroplasty groups were performed with Wilcoxon's rank sum test. Statistically significant probability values are given in bold.

The differences in inflammatory response to hip and knee arthroplasty remain interesting research questions, although there might be more factors resulting in different response patterns than the damage to the bone, bone marrow and soft tissues alone, e.g., bone cement, which was shown to activate the complement system [14]. Further studies on both THAs and TKAs with and without bone cement would be necessary to answer this question.

There was also a difference in CRP response pattern in patients with normal and elevated BMI. This finding is consistent with previous studies [15].

Cytokine release is the initiating step in the immune response after various inflammatory stressors. In fact, it precedes the CRP production [1]. This was also confirmed by the analysis of temporal patterns of IL-6 and CRP in our study. Mannick et al. also reported a correlation between the serum concentrations of IL-6 and CRP after elective orthopedic surgery [16]. IL-6 is produced by monocytes and macrophages in response to a local infection and it triggers the synthesis of CRP in the liver [17–19]. A potential advantage of measurements of IL-6 lies in the fact that its level returns to normal within 48 h of surgery [20–22].

In our study, IL-6 revealed a distinct postoperative pattern after arthroplasty with abrupt rise and a quick, monophasic decline. In the literature, IL-6 peaks in the first 6–12 h after surgery and decreases to its baseline range by 48–72 h postoperatively after THA or TKA [21, 22]. We observed similar kinetics in hip and knee procedures, however, the magnitude of response was higher in TKA group. This observation, along with the fact that the use of minimally invasive and inflammatory modulating approaches in total joint replacement is on the rise could serve as an interesting point for further studies. Once we establish the causes and significance of differences in inflammatory response, we could better tailor the modulation of inflammatory response in order to decrease long-term complications, such as persistent pain and fibrosis [4].

The independence of IL-6 from the body mass index is an unexpected finding of this study. Obesity is characterized by chronic inflammation and elevated IL-1 and IL-6 levels, among other cytokines [15]. The fact that the CRP response is altered by increased body weight, whereas IL-6 is not, could be explained by the fact that obese patients, functioning on the metabolic surplus can mount more marked inflammatory response to major surgery, which would be evident in CRP levels, as its production is liver function – dependent [23]. This finding could be also important for clinical practice. Discharge data from CDC showed more than 100% increase of obesity incidence in patients undergoing THA between years 1990 and 2004 in the US [24]. Therefore, an inflammatory marker, which would be independent from BMI, could clearer describe the inflammatory status and the effects of anti-inflammatory treatment used in total joint replacement. We believe to present the first study with the finding of similar IL-6 response patterns in obese and normal weight patients in the early postoperative period. There was, however, a study by Gletsu et al., in which they found increased postoperative IL-6 plasma concentrations in severely obese patients undergoing abdominal surgery [17]. The difference in results might stem from the fact that 1) all the obese patients in their study had BMI>40 kg/m^2 and 2) the response to abdominal surgery might be provoked by different factors than in bone and joint surgery, as even for THA and TKA, response patters differ significantly. The only study performed on orthopedic patients (60 primary THAs) by Motaghedi et al. found no increase in postoperative circulating cytokine levels, including IL-6, in obese patients. However, only single postoperative measurement was performed and thus, their results do not provide a comprehensive description of inflammatory response [25].

The changes in IL-1β and IL-8 concentrations were either random or attributable to other factors than total joint replacement. This finding supports the earlier results [26]. We believe that there is no relationship between surgical trauma and both IL-1β and IL-8 serum concentrations, or that a correlation – if any – may either occur at the local level of the surgical wound or at very short intervals. The work of Bottner et al., who reported an increased concentration of IL-8 in synovial fluid harvested as washed wound drainage from patients who had undergone TKA would support this theory [27].

NT-proCNP is more stable and is in higher serum level than the active form of CNP hormone, therefore seemed to be a more reliable biomarker [28]. NT-proCNP has been recently investigated to be a potential inflammatory biomarker in rheumatoid arthritis [29]. Our study results

showed that its level changes were insignificant. Most probably, the surgical trauma, which primarily is a local inflammation trigger, does not cause NT-proCNP concentration changes as do generalized stimuli, like severe sepsis [30].

The major limitation of our study lies in the fact that the only way to distinguish between changes from postsurgical trauma and other sources of inflammation, including infection, was done post-factum. This distinction was carried out on the basis of not fulfilling the CDC surgical site infection criteria up to 2 years after the index surgery and – as every retrospective measurement – is prone to the examiner's error. However, we feel that 2-year follow up is sufficient to confidently rule our infection, even caused by slow-growing, biofilm-producing bacteria [31].

An important limitation of this study is that we did not compare two completely matched groups, which rendered impossible in-depth analysis of the influence of comorbidities and clinical events, such as hypovolemia and blood transfusion, on inflammatory response [2]. Also, the observational nature of our study does not allow us to claim causative link between obesity and inflammatory markers. We feel though, that our study setup, with the recruitment of consecutive, non-selected patients, resembles one of the everyday clinical practice and therefore – to some extent – our findings could be extrapolated to the general situation.

The present study with multi-cytokine analysis at multiple time-points, both pre- and postoperatively, following THA and TKA, demonstrated an elevation in CRP with only a minor, non-significant response of IL-1β, IL-8 and NT-proCNP. We describe results of IL-6, as compared to routinely used marker, CRP, as advantageous in clinical setting due to similar kinetics with faster dynamics of change and the fact that it is not influenced by patients' body weight, as is CRP. Both markers – CRP and IL-6 – differed significantly between hip and knee patients. The measurement of AUC, as opposed to the multiple comparisons of separate values taken at different time points, provides clearer insight into the magnitude of inflammatory response.

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