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Sex Differences in Serum C-Reactive Protein Course after Total Hip Arthroplasty

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Background: Gender-specific medicine has become an important part in investigating the course of various diseases. C-reactive protein (CRP) is used as an inflammatory marker for detecting inflammations and even infections after total hip arthroplasty (THA). The general course of CRP after THA is well known, but there is controversy about its association with sex. Therefore, we aimed to investigate if there is an influence of sex on the CRP after THA in the first 10 days after operation in a complication-free course in male and female patients and to re-evaluate the specific postoperative CRP course with its maximum on the second to third postoperative days.

Methods: We retrospectively reviewed patients who had been treated with THA due to primary osteoarthritis through the same approach using an equal model of a cementless stem and a cup and complication-free between 2013 and 2016. Patients with active inflammation, rheumatoid arthritis, secondary arthrosis, active cancer disease, and documented postoperative complications were not included. The CRP values before THA and up to 10 days after THA were recorded and tested for sex discrepancy. Factor analyses were performed, and CRP values were adjusted for confounders (age, operation time, diabetes mellitus, and body mass index [BMI]).

Results: A total of 1,255 patients (728 women and 527 men) were finally analyzed. Men were younger and had a longer operation time and a higher BMI compared to women. The prevalence of overweight was higher in men, while obesity (BMI > 40 kg/m^2), diabetes mellitus, renal failure, and American Society of Anaesthesiologists status showed no significant difference between men and women. Men had significantly higher CRP values than women between the 2nd and the 7th postoperative days, with the largest difference on the 4th postoperative day (men, 130.48 mg/L; women, 87.26 mg/L; $p = 0.018$).

Conclusions: Based on the results of more precise sex-specific evaluation of the postoperative CRP course after THA, the present study showed for the first time that there was a gender discrepancy in the CRP course after complication-free THA in the first 7 postoperative days. Furthermore, this study confirmed the postoperative CRP course with its maximum on the third postoperative day.

Keywords: *Hip replacement arthroplasty, Gender, C-reactive protein, Prosthesis-related infections, Sex characteristics*

Total hip arthroplasty (THA) is a common operation and septic postoperative complications are rare. Nevertheless, prosthetic joint infection (PJI) is still a serious complication of hip arthroplasty with an incidence of 0.3% to 1.7% despite a decrease in the last decades because of improvements in prosthetic designs, operation procedures, and optimized materials.[1,2)]

To detect postoperative PJI, the C-reactive protein

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(CRP) value is commonly used for investigating the inflammation course after THA.[3-5] CRP, an acute-phase protein, is predominantly produced by hepatocytes and triggered by interleukin-6 (IL-6). It has a very low blood plasma concentration (0.8 mg/L to 3.0 mg/L) in healthy adults and is rapidly elevated in case of acute inflammation, infection, malignancy, and traumatic injury or surgery. Moreover, CRP has a long half-life and stable levels with negligible circadian variation.[6] The CRP course after THA has been well investigated. It shows a characteristic increase within a few hours and a maximum value between the second and third postoperative days. Subsequently, it slowly falls to the preoperative level, lasting 3–6 weeks in case of a complication-free postoperative course.[7] However, there has been a controversy in the literature on the potential influence of sex on the postoperative CRP course after THA with the emergence of gender-specific medicine.[4,8,9] The knowledge of the complication-free CRP course is decisive to predict whether there is a coexisting infection. In this context, an anthropometric investigation showed first hints of sex-specific CRP courses independent from specific operations.[10]

The aim of this study was to test the hypothesis that sex influences the postoperative CRP course in the first 10 days after THA and to re-evaluate the characteristic CRP maximum on the second or third postoperative day after a complication-free THA.

METHODS

Ethical Approval

Ethical approval has been done by the independent Ethics Committee of the Medical Faculty at the Friedrich Schiller University of Jena, Germany (No. 2018-1118). Informed consent from patients was waived due to retrospective nature of this study. Informed consent from patients was obtained at inpatient admission for data analysis.

We retrospectively reviewed 1,255 patients who received cementless THA (CLS Spotorno Stem, Allofit, Allofit-S, Allofit classic cup; Zimmer Biomet Deutschland, Freiburg Breisgau, Germany) due to primary osteoarthritis between January 2013 and December 2016 in the Orthopaedic Department of the Waldkliniken Eisenberg, Orthopaedic Professorship of the University Hospital Jena. Patients who had an active inflammation, active rheumatoid arthritis, active cancer disease, or an inflammatory disease and patients with peri- and postoperative complications (registered late and early PJI or surgical site infections [SSIs], revision, fractures, urinary or bowel infections, and pulmonary embolism) were not included. After ensuring the diagnosis of primary osteoarthritis, all patients were treated with the same surgical approach (modified lateral approach [Bauer's approach]) in the same hospital under general anesthesia by senior surgeons (ER, CW, SB, and GM). All patients received a standardized preoperative single-shot antibiotic with cephazolin or clindamycin and underwent a standardized postoperative mobilization and physiotherapy (resting in bed on the operation day; day 1, rising from bed and first steps with crunches for mobilization in the room and behavioral education; days 2 and 3, walking in the corridor, enhancing distance; day 4, stair training; and day 5, enhancing distance). The CRP values were recorded in the clinical information system (Orbis; Agfa HealthCare, Bonn, Germany) before and up to 10 days after THA and were retrospectively analyzed according to patient sex.

The CRP value was measured in the hospital's own laboratory using a qualitative visual latex agglutination test. A pathologic CRP was defined as higher than 5 mg/L (0.5 mg/dL). The effective measuring range of the method used was estimated at the interval from 0.3 mg/L to 350 mg/L. The lowest limit of detection was 0.2 mg/L, and the lowest identification threshold was 0.3 mg/L. The effective measuring range and identification threshold were determined according to the explicit requirements of the medical device directive EP17-A of the Clinical and Laboratory Standards Institute.

Statistical analysis was performed with IBM SPSS ver. 27 (IBM Corp., Armonk, NY, USA). As an analytical approach, nonparametric tests of two samples were chosen. Mann-Whitney *U*-test and chi-square test were performed as a suitable statistical analytical procedure for comparing two groups. The level of significance was $p < 0.05$. To investigate the potential influence of confounders, we did a factor analysis including demographic data (age and body mass index [BMI]), surgery time, the American Society of Anesthesiologists (ASA) physical status, and patients' diseases (overweight [BMI ≥ 35 kg/m²], obesity [BMI ≥ 40 kg/m²], diabetes mellitus, renal failure [Kidney Disease: Improving Global Outcomes score ≥ 3], and osteoporosis). Confounders with a significant association were considered for univariate linear regression models.[11]

RESULTS

A total of 1,499 patients were enrolled in the study. Of these, 134 were not included because of diseases mentioned above and 110 were excluded because of peri- and postoperative complications; ultimately, 1,255 patients were available for final analysis (Fig. 1). There were 527

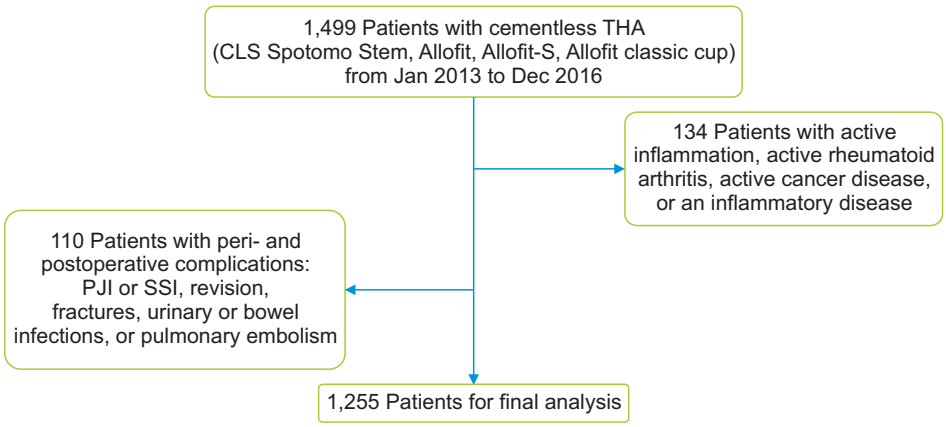

Fig. 1. Flowchart of patient enrolment. THA: total hip arthroplasty, PJI: prosthetic joint infection, SSI: surgical site infection.

Table 1. Baseline Characteristics

Variable	Male	Female	*p*-value
Total number	527 (42)	728 (58)	-
Age (yr)	67.85 ± 9.58	69.43 ± 8.59	0.007
BMI (kg/m²)	29.04 ± 4.55	28.51 ± 5.19	0.009
Operation time (min)	69 ± 21	65 ± 20	0.003
ASA score I	32 (6.1)	23 (3.2)	-
ASA score II	347 (66.0)	533 (73.4)	-
ASA score III	147 (27.9)	170 (23.4)	-
ASA value	2.2 ± 0.48	2.22 ± 0.54	0.414
Diabetes mellitus	94 (17.8)	105 (14.4)	0.102
Overweight (BMI > 35 kg/m²)	435 (82.5)	541 (74.3)	0.001
Obesity (BMI > 40 kg/m²)	195 (37.0)	250 (34.3)	0.331
Renal failure (KDIGO score ≥ 3)	15 (2.8)	15 (2.1)	0.368
Osteoporosis	12 (2.3)	59 (8.1)	0.001

Values are presented as number (%) or mean ± standard deviation.
BMI: body mass index, ASA: American Society of Anesthesiologists, KDIGO: Kidney Disease: Improving Global Outcomes.

men (42%) and 728 women (58%) who had been treated with THA from January 2013 to December 2016 (Table 1). Baseline characteristics are shown in Table 1. Male patients were younger ($p = 0.007$) and had higher BMI ($p = 0.009$). The operation time was longer in men ($p = 0.003$) and male patients suffered more often from overweight ($p = 0.001$), while female patients suffered more often from osteoporosis ($p < 0.001$). The frequency of diabetes mellitus, obesity, and renal failure and ASA score did not differ significantly. The CRP course is shown in Table 2. The factor analysis including patients' baseline characteristics showed there was an influence of BMI, age, diabetes mellitus, and operation time on patients' serum CRP levels and thus were considered for adjustment.

The preoperative CRP showed no difference between male and female groups. A significant difference between the two sex groups emerged from the third to the seventh postoperative day in the mean CRP before and after adjustment for age, BMI, diabetes mellitus, and operation time, with a significantly elevated course for men with the largest difference on the fourth postoperative day (Fig. 2, Table 2). When subdivided according to age and BMI, the CRP value showed a significant difference between the two sex groups on day 3 in all age groups, on days 5 to

Table 2. CRP Course, Crude and Adjusted Level of Significance

Day	Male (mg/L)	Female (mg/L)	Crude *p*-value	Adjusted *p*-value
Preoperative	2.94 ± 02.29	3.05 ± 02.29	0.156	0.247
1	56.12 ± 49.36	50.16 ± 25.16	0.425	0.681
2	133.89 ± 61.54	112.13 ± 53.67	0.048	0.198
3	141.30 ± 74.83	120.21 ± 59.72	< 0.001	0.001
4	130.48 ± 76.22	87.26 ± 56.05	0.018	0.038
5	78.82 ± 48.89	61.17 ± 55.49	< 0.001	0.046
6	59.68 ± 35.69	46.86 ± 27.43	< 0.001	0.049
7	44.27 ± 28.65	36.32 ± 26.56	< 0.001	0.021
8	51.43 ± 32.99	45.96 ± 41.89	0.240	0.902
9	51.97 ± 38.22	49.55 ± 37.52	0.799	0.836
10	40.14 ± 27.94	49.88 ± 38.71	0.781	0.805

Values are presented as mean ± standard deviation.
CRP: C-reactive protein.

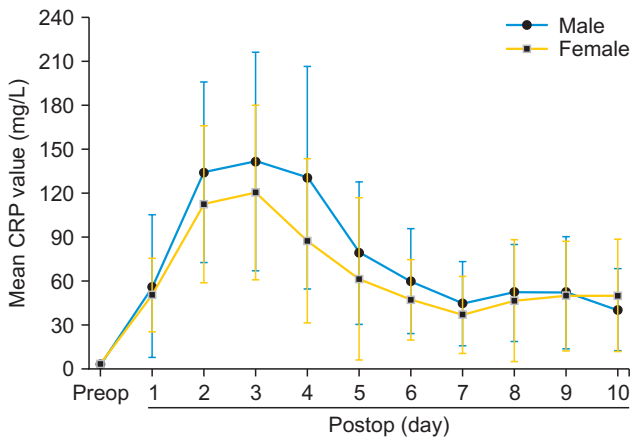

Fig. 2. Comparison of sex-specific patterns of mean C-reactive protein (CRP) values from preoperative (Preop) day to postoperative (Postop) days 1–10.

7 in those between 65 and 90 years of age, on days 3 and 6 in those with BMI ≤ 25 to 35 kg/m², on day 5 in those with BMI 25 to 45 kg/m², and on day 7 in those with BMI 25 to 35 kg/m² (Table 3). After THA, the CRP value for all patients increased significantly and achieved its maximum on the third postoperative day, then approaching the lowest value after 7 days and a second increase to day 10 (Table 2).

DISCUSSION

In our retrospective study, we observed sex discrepancy in the CRP course on the first days after THA (Fig. 1) and confirmed available hints on the influence of patient sex after THA.[10] Confounders including BMI, overweight, age, operation time, and diabetes mellitus were partially known as modulators of CRP.[12-14] After the factor analysis and adjustment, the CRP level was still significantly elevated in male patients in our study, so patient sex seems to have an independent effect on the CRP course. Even after the subdivision according to age and BMI, there was a significant influence of sex on the CRP level among all groups on day 3 and almost all groups on day 5 to 7 (Table 3). Furthermore, despite the knowledge about the influence of BMI on CRP, male patients with significantly higher BMI showed no difference in preoperative CRP in our study.

In contrast to Larsson et al.,[8] who described no gender specificity of CRP after THA, our study showed a significant difference in the CRP level according to sex after treating patients with an artificial hip joint before and after adjustment for confounding factors. It was assumable that the CRP level was exclusively a marker of aseptic inflammation because patients with active inflammatory disease, SSI, PJI, and other postoperative complications and infections were not included in our study. It was confirmed in our study that the CRP course was higher in men as had already described for total knee arthroplasty[15] and spine

Table 3. CRP Course for Different Age and BMI Ranges and Level of Significance

Day	Age (yr)	CRP (mg/L)			BMI (kg/m²)	CRP (mg/L)		
		Male	Female	*p*-value		Male	Female	*p*-value
Preop	≤ 60	3.09 ± 2.62 (116)	3.41 ± 2.58 (124)	0.222	≤ 25	2.34 ± 2.05 (93)	2.19 ± 2.03 (186)	0.458
	61–75	2.79 ± 2.20 (295)	3.06 ± 2.24 (432)	0.061	> 25–35	2.97 ± 2.31 (383)	3.17 ± 2.24 (470)	0.058
	76–90	2.95 ± 2.30 (150)	2.87 ± 2.24 (232)	0.749	> 35–45	3.41 ± 2.45 (52)	4.26 ± 2.49 (72)	0.044
	> 90	NA	NA	NA	> 45	1.2 ± 0.00 (1)	3.93 ± 1.77 (6)	0.286
1	≤ 60	57.00 ± 24.09 (28)	53.48 ± 22.60 (27)	0.631	≤ 25	55.42 ± 24.99 (16)	44.79 ± 18.91 (39)	0.214
	61–75	59.72 ± 61.62 (65)	46.18 ± 25.76 (68)	0.101	> 25–35	57.11 ± 54.12 (88)	53.38 ± 26.94 (74)	0.975
	76–90	49.78 ± 28.34 (32)	54.02 ± 23.96 (42)	0.332	> 35–45	50.56 ± 27.97 (10)	53.08 ± 29.25 (13)	0.784
	> 90	NA	NA	NA	> 45	13.90 ± 0.00 (1)	28.87 ± 8.72 (3)	0.500
2	≤ 60	134.22 ± 55.77 (19)	107.25 ± 51.27 (23)	0.109	≤ 25	130.04 ± 61.23 (13)	103.19 ± 45.20 (22)	0.216
	61–75	132.81 ± 66.91 (29)	101.30 ± 46.57 (39)	0.091	> 25–35	133.31 ± 62.50 (43)	113.06 ± 55.12 (54)	0.157
	76–90	145.79 ± 62.52 (14)	137.06 ± 62.48 (20)	0.641	> 35–45	165.10 ± 0.00 (1)	145.78 ± 68.54 (6)	1.000
	> 90	NA	NA	NA	> 45	84.80 ± 0.00 (1)	NA	NA
3	≤ 60	131.86 ± 107.87 (95)	106.92 ± 54.07 (103)	0.047	≤ 25	124.55 ± 59.94 (78)	107.62 ± 53.64 (164)	0.031
	61–75	138.61 ± 63.96 (260)	116.72 ± 59.21 (382)	< 0.001	> 25–35	144.90 ± 79.33 (330)	123.65 ± 60 (404)	< 0.001
	76–90	151.39 ± 61.60 (131)	136.95 ± 63.45 (206)	0.021	> 35–45	142.91 ± 61.22 (51)	127.81 ± 64.69 (65)	0.026
	> 90	NA	NA	NA	> 45	79.60 ± 0.00 (1)	143.10 ± 88.62 (5)	0.667
4	≤ 60	86.32 ± 47.00 (6)	67.55 ± 41.84 (6)	0.485	≤ 25	85.74 ± 32.24 (5)	77.71 ± 41.39 (10)	0.768
	61–75	121.88 ± 65.31 (12)	74.66 ± 36.50 (18)	0.048	> 25–35	141.18 ± 81.45 (19)	88.87 ± 56.43 (19)	0.023
	76–90	172.21 ± 85.91 (9)	136.56 ± 82.31 (7)	0.470	> 35–45	140.60 ± 96.17 (2)	118.37 ± 87.18 (3)	1.000
	> 90	NA	NA	NA	> 45	NA	34.30 ± 0.00 (1)	NA
5	≤ 60	58.52 ± 34.69 (27)	79.57 ± 96.02 (24)	0.713	≤ 25	66.65 ± 35.78 (17)	66.08 ± 74.96 (40)	0.346
	61–75	91.69 ± 54.62 (47)	48.83 ± 25.37 (64)	< 0.001	> 25–35	78.72 ± 52.67 (62)	60.07 ± 42.35 (69)	0.015
	76–90	75.81 ± 34.09 (16)	65.24 ± 51.62 (36)	0.117	> 35–45	111.74 ± 13.52 (5)	50.01 ± 45.13 (8)	0.030
	> 90	NA	NA	NA	> 45	NA	34.10 ± 3.96 (2)	NA
6	≤ 60	47.90 ± 29.18 (61)	44.47 ± 29.43 (69)	0.393	≤ 25	52.41 ± 33.37 (55)	41.72 ± 25.26 (98)	0.023
	61–75	60.14 ± 34.94 (178)	45.17 ± 27.18 (250)	< 0.001	> 25–35	62.71 ± 36.68 (227)	47.67 ± 26.42 (274)	< 0.001
	76–90	66.86 ± 37.67 (90)	51.39 ± 28.49 (143)	0.001	> 35–45	49.08 ± 28.31 (30)	51.87 ± 34.30 (49)	0.852
	> 90	NA	NA	NA	> 45	NA	50.40 ± 35.17 (5)	NA
7	≤ 60	35.01 ± 29.37 (51)	34.02 ± 29.51 (49)	0.667	≤ 25	39.24 ± 26.04 (38)	34.57 ± 27.19 (73)	0.186
	61–75	44.13 ± 27.70 (121)	36.55 ± 26.10 (165)	0.008	> 25–35	45.39 ± 29.67 (160)	36.58 ± 25.91 (174)	0.002
	76–90	50.75 ± 27.33 (65)	38.51 ± 27.05 (79)	0.002	> 35–45	44.49 ± 24.49 (21)	40.87 ± 29.77 (23)	0.526
	> 90	NA	NA	NA	> 45	15.70 ± 0.00 (1)	34.27 ± 29.25 (3)	0.500

Table 3. Continued

Day	Age (yr)	CRP (mg/L)			BMI (kg/m²)	CRP (mg/L)		
		Male	Female	*p*-value		Male	Female	*p*-value
8	≤ 60	62.69 ± 41.33 (7)	33.43 ± 26.44 (6)	0.181	≤ 25	54.73 ± 34.17 (6)	50.49 ± 43.88 (10)	0.562
	60–75	45.08 ± 30.60 (11)	32.40 ± 24.32 (15)	0.259	25–35	49.18 ± 33.72 (20)	44.09 ± 44.09 (21)	0.348
	75–90	50.54 ± 30.62 (10)	67.40 ± 55.12 (13)	0.483	35–45	64.05 ± 38.25 (2)	36.90 ± 27.47 (4)	0.533
	> 90	NA	NA	NA	> 45	NA	33.40 ± 0.00 (1)	NA
9	≤ 60	83.5 ± 48.93 (2)	49.18 ± 56.91 (4)	1.000	≤ 25	55.64 ± 31.22 (5)	74.00 ± 48.38 (4)	0.730
	60–75	42.03 ± 40.53 (8)	36.64 ± 31.65 (8)	1.000	25–35	49.78 ± 42.98 (13)	48.21 ± 36.54 (9)	0.896
	75–90	53.81 ± 34.63 (9)	56.56 ± 32.15 (8)	0.963	35–45	61.1 ± 0.00 (1)	31.62 ± 27.87 (4)	1.000
	> 90	NA	NA	NA	> 45	NA	35.50 ± 0.00 (1)	NA
10	≤ 60	64.25 ± 72.62 (2)	35.70 ± 0.00 (1)	1.000	≤ 25	31.10 ± 6.93 (2)	107.8 ± 0.00 (1)	0.667
	60–75	43.49 ± 19.61 (7)	23.28 ± 20.37 (5)	0.073	25–35	43.61 ± 30.66 (11)	64.42 ± 38.18 (6)	0.216
	75–90	25.80 ± 8.70 (5)	74.41 ± 38.65 (6)	0.030	35–45	20.00 ± 0.00 (1)	20.25 ± 10.77 (4)	1.000
	> 90	NA	NA	NA	> 45	NA	23.30 ± 0.00 (1)	NA

Values are presented as mean ± standard deviation (number).
CRP: C-reactive protein, BMI: body mass index, Preop: preoperative, NA: not available (no patients beyond 90 years or BMI > 45 kg/m²).

surgery.[16]

The reason for this postoperative sex discrepancy in CRP course is still unclear. Siennicka et al.[17] postulated there was a variation in inflammatory and hemostatic response after acute coronary syndrome between men and women. They investigated the serum-levels of inflammatory and hemostatic markers in patients after acute coronary syndrome and observed a higher CRP and IL-6 level in male patients, consistent with previous findings explained by hemostatic and inflammatory pathways, which have a higher activation and feedback cycle in men than in women.[18] Also, Sperry and Minei[19] reported a higher IL-6 level after traumatic injury and hemorrhagic shock in men. Furthermore, Angele et al.[20] reported an effect of sex hormones on immune response after trauma, specifically a decreased anti-inflammatory response generated by higher testosterone levels in men[19,21] Pace et al.[22] also showed sex differences in the increase of production of prostaglandin and elevated cyclooxygenase (Cox-2) expressions connected with increased nuclear factor kappa B activation in male mice and rats after induced pleurisy and peritonitis.[22] Bohl et al.[23] pointed out the male sex as a risk factor for postoperative sepsis after total joint arthroplasty, supporting the thesis that an inflammatory response after surgery is gender-dependent. Schroder et al.[24] reported more anti-inflammatory mediators in women than men with a sepsis caused by a gender-specific inflammatory answer. In conclusion, the sex-specific hormone status seems to have a high impact on the anti-inflammatory homeostasis and the postoperative CRP level.

Surgical trauma also seemed to have influence on the CRP level.[25] This could explain the differences in CRP course in different operations and localisations.[26] Larsson et al.[8] showed a tissue-dependent postoperative increase in CRP in bone, fat, or muscle because of a different concentration of macrophages, which are more common in bone marrow than in fat and muscle tissue, triggering an inflammatory response by releasing IL-6.[8] Consistent with this, Shen et al.[5] reported lower CRP values were observed after resurfacing the femoral head, compared to conventional THA, since the femoral medullar space is not open if the head is just resurfaced. Watt et al.[9] showed a higher CRP level correlating with an increased surgical trauma. In conclusion, it may be assumed that larger tissue damage during the surgical procedure in men could explain the higher CRP level. Studies investigating sex-specific tissue damage after THA are actually not available. Theoretically a higher mass of active bone marrow in bigger male bones with more stimulator cells (macrophages and platelets) releasing pro-inflammatory mediators can be explained by higher body height in male patients.[27]

Furthermore, male patients were younger, had a

longer operation time, and higher BMI with a higher prevalence of overweight (but not obesity). Basques et al.[28] already demonstrated a slightly increased operation time in a male study group after total hip and knee arthroplasty. This could be explained by the fact that men often have larger hips than women.[29,30] Therefore, a more voluminous surgical approach for male patients could be needed. The differences in the anatomic dimensions of the hip between men and women, the higher BMI in men in our study group, and the perhaps associated larger surgical approach could reasonably explain the slightly increased operation time in male patients undergoing THA.

Our analysis confirmed the complication-free postoperative CRP course after THA described in the literature. It showed a rapid postoperative increase with the highest CRP values from the second to the third postoperative day[3-5] (Fig. 1). After reaching the peak, the CRP values returned slowly to a normal range, lasting 3 to 8 weeks.[31] In our study, the CRP level increased again after the seventh day, which may be due to testing bias. Patients with higher values in the postoperative course were tested longer and dismissed later, so only patients with an elevated course provided data for the late course.

Limitations of our study were the retrospective study design and analysis, the limited surveillance of a maximum of 10 days after THA, and the decreasing amount of data on days 2, 4, and after day 7 because of earlier discharge from hospital and missing blood samples. Because of this limitation, we could not evaluate the late postoperative period CRP course and its return to a normal range and values on days 2, 4 and 7 to 10 should be interpreted carefully. Also, other established inflammatory markers were not measured in our study to confirm their course. Furthermore, smoking[32] and weather[33] during hospital stay and operation day as CRP-influencing factors were not investigated. The treatment with anti-inflammatory drugs and immune modulatory drugs was also not investigated but rheumatoid disease was excluded from the study. Another limitation is the lack of investigation of the exact size of the approach and resultant tissue damage as a potential influencing factor on the CRP course. Still, we think that our results are useful in the day-by-day clinical practice when interpreting postoperative CRP values in female and male patients with uncomplicated THA.

In summary, we could show that the complication-free course of CRP after THA was sex-specific during the first 7 postoperative days with higher CRP values observed in men than women. Also, the operation time was increased in the male study group. The impact of these results on diagnosis is a more precise sex-specific interpretation of the postoperative complication-free CRP course after THA. Therefore, surgeons should always take into consideration of patient's sex for better risk evaluation and patient safety.

CONFLICT OF INTEREST

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

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