

# Evaluation of serum levels of C-reactive protein after total knee arthroplasty in patients with rheumatoid arthritis

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## Abstract

**Objective:** The objective of this study is to evaluate the serum levels of C-reactive protein in the first three weeks after total knee arthroplasty, in patients with knee osteoarthritis secondary to rheumatoid arthritis and a control group. **Methods:** This is a prospective study evaluating 30 patients with knee osteoarthritis secondary to rheumatoid arthritis who underwent total knee arthroplasty between January 2015 and March 2017. A control group of patients submitted to total knee arthroplasty by primary osteoarthritis was created with data from the institution's database. The proportion was of three controls for each case and the criteria used for pairing were age, gender, ethnicity and body mass index. Serum C-reactive protein was measured on the day before, and on the third and twenty-first days after the procedure in all patients. **Results:** No statistically significant changes were found between the case and control groups for the C-reactive protein levels evaluated nor their variations. The results suggest that the presence of rheumatoid arthritis does not interfere in the postoperative response of C-reactive protein. **Conclusion:** The serum values of C-reactive protein after TKA do not differ between patients with primary or secondary osteoarthritis to RA. Thus, the reference values can be considered equal in both cases.

**Keywords:** Knee; Arthroplasty; CPR; Osteoarthritis; Rheumatoid arthritis.

## Introduction

Rheumatoid arthritis (RA) is a chronic and progressive systemic inflammatory disease that affects the synovial membrane,<sup>1</sup> generating a complex inflammatory process with synovial proliferation and recurrent effusions, causing joint destruction in its final stages.<sup>2,3</sup>

Total knee arthroplasty (TKA) has become the most common orthopedic intervention in patients with osteoarthritis (OA) secondary to RA,<sup>2</sup> since this procedure restores mobility, while providing functional recovery and pain relief.<sup>3</sup>

C-reactive protein (CRP) is an acute-phase protein with both anti- and pro-inflammatory properties.<sup>4</sup> Acute phase proteins vary by at least 25% from their baseline serum value during inflammatory processes.<sup>5</sup> CRP is

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synthesized and secreted by hepatocytes within 4 to 6 hours after an initial stimulus. Its serum concentration doubles every 8 hours, reaching a peak between 36 and 50 hours. It has a half-life of 19 hours and takes several days to return to baseline values.<sup>6</sup> The measurement of serum CRP is part of the initial clinical evaluation in the context of persistent postoperative pain in patients undergoing TKA, in cases where an infectious process is suspected.<sup>7</sup> One study shows that RA patients have an increased incidence of infection after TKA.<sup>3</sup>

RA patients generally have higher baseline concentrations of CRP,<sup>8</sup> and it is essential to know the physiological behavior of patients with underlying diseases, in order to avoid diagnostic errors and unnecessary treatments. Serum CRP has a prognostic value in the treatment of RA, being directly associated with failure to treat rheumatological disease.<sup>9</sup>

The aim of the study was to assess serum levels of C-reactive protein in the first three weeks after total knee arthroplasty in patients with osteoarthritis of

the knee secondary to rheumatoid arthritis and in a control group.

## Methods

After receiving approval of the research study from the Research Ethics Committee of the institution (under CAAE nr. 60196916.5.0000.5273), 120 individuals submitted to TKA were prospectively evaluated and monitored for 21 days. The research took place between January 2015 and March 2017. The case group consisted of 30 patients submitted to TKA for OA secondary to RA and the control group was composed of 90 patients submitted to the same procedure for primary OA.

Prospective and conveniently included patients were aged 40 years or older, had secondary knee OA and met the criteria of the Consensus of the Brazilian Rheumatology Society for the diagnosis of RA.<sup>1</sup> The patients in the case group were evaluated at the institution's rheumatology outpatient clinic.

The control group consisted of patients undergoing TKA due to primary OA, chosen from the institution's database. The proportion used was three controls for each case and the criteria used for matching were: age, sex, ethnicity, body mass index (BMI) and comorbidities.

All patients in the research agreed to participate by signing an Informed Consent Form. The patients were operated on by surgeons belonging to the knee surgery group.

Patients submitted to another surgical procedure; with an infectious condition outside the operations site within 6 weeks before TKA; who abandoned the follow-up; or did not perform the three collections on the stipulated dates were excluded from the sample.

Patients followed the institution's usual surgical protocol, including preoperative outpatient assessment to check routine or specific exams and anesthetic release, hospitalization on the eve of surgery, spinal anesthesia associated with local femoral and sciatic nerve block, intravenous antibiotic prophylaxis 30 minutes before the start of the procedure, use of a pneumatic tourniquet during the procedure, with release for hemostasis control after cementation, total cemented knee prosthesis implants, with cement without the addition of antibiotics and replacement of the patella, use of a hemovac drain (removed 24 hours after surgery), early walking on the second postoperative day, using a walker, prophylaxis against

deep vein thrombosis (DVT) with 40mg Enoxaparin, a subcutaneous dose once daily for 21 days.

The analysis of serum CRP was performed using a 2 ml sample of venous blood evaluated by the turbidimetric method on the BT3000 Plus® biochemistry analyzer (Wiener Lab - Rosário, Santa Fé, Argentina), with a reference limit in adults of 5 mg/L. The dosage on the day before surgery was called CRP<sub>0</sub>. On the third day after operation, with the patient still in hospital, a new sample was collected for analysis, called CRP<sub>3</sub>. Patients were discharged according to clinical criteria, including: good pain control; operative wound in good condition; vital signs; blood count; renal function and normal electrolytes. The first review appointment was scheduled on the 21st day after operation to collect the sample called CRP<sub>21</sub>, before any consultation or manipulation of the wound. All exams were collected and evaluated in the institution's laboratory.

From the data collected, a database was built, stored in a Microsoft Excel 2007 electronic spreadsheet, which was analyzed using the SPSS (Statistical Package for the Social Sciences) program version 22.0. For sample characterization and descriptive analysis of the behavior of the variables, the data were synthesized through the calculation of descriptive statistics (mean, median, minimum, maximum, standard deviation, coefficient of variation (CV) and proportions of interest), simple frequency distributions and in cross tables. The variability in the distribution of a quantitative variable was considered low if CV < 0.20, moderate if CV was between 0.20 and 0.40, and high if CV ≥ 0.40.

From the CRP<sub>0</sub> and CRP<sub>3</sub> measurements, the first CRP variation ( $\Delta_1$ CRP) is given by

$$\Delta_1\text{CRP} = \frac{\text{CRP}_3 - \text{CRP}_0}{\text{CRP}_0} \times 100$$

The  $\Delta_1$ CRP measures the percentage of increase or decrease in CRP<sub>0</sub> that occurred in the first 3 days after surgery.

From the CRP<sub>3</sub> and CRP<sub>21</sub> measurements, the second CRP variation ( $\Delta_2$ CRP) is given by

$$\Delta_2\text{CRP} = \frac{\text{CRP}_{21} - \text{CRP}_3}{\text{CRP}_3} \times 100$$

The  $\Delta_2$ CRP measures the percentage of increase or decrease in CRP<sub>3</sub> that occurred between the third and twenty-first day after surgery. CRP<sub>21</sub> was considered normal when it reached a value less than or equal to 5 mg/L or a value less than or equal to CRP<sub>0</sub>.

The chi-square test was used in the inferential analysis to verify the significance of the association between two qualitative variables. When this proved inconclusive and the situation was appropriate, Fisher's exact test was used. In the inferential analysis of quantitative variables, the hypothesis of normal distribution was verified by the Kolmogorov-Smirnov and Shapiro Wilk tests. When the hypothesis of normal distribution was not rejected in the groups by the two tests, the comparison of the two independent groups was made using Student's t test. The equality of variances, necessary to perform Student's t test without correction, was assessed by the Levene test.

For any of the groups, when the hypothesis of normality of the distribution was rejected by any of the normality tests, the comparison of the two groups was made by the non-parametric Mann-Whitney test. Two repeated measures were compared using the paired Student's t test when distribution was normal or the Wilcoxon test when non-normal.

The investigation of the correlation between two quantitative variables used a parametric approach, by calculating Pearson's linear correlation coefficient, when the variables had a normal distribution or non-parametric approach, or by calculating Spearman's correlation coefficient, when at least one of the variables did not present a normal distribution. The t test for the correlation coefficient was used to assess the significance of the calculated correlation coefficients. All discussions were carried out considering a maximum significance level of 5% ( $p < 0.05$ ). For tests that provided asymptotic and exact p-values, the exact p-values were taken into account.

A secondary evaluation was carried out in the RA group to verify whether there is any influence of the dose of corticosteroids used in patients during the pre-, peri and postoperative periods on the values of the serum CRP and its variations.

## Results

The sample distribution was not homogeneous in relation to gender. In the case group, 28 (93.3%) patients were female and 2 (6.7%) were male. In the control group, 69 patients (76.7%) were female and 21 were male (23.3%). There was a significant predominance of women in the case group ( $p = 0.045$ ).

As for laterality, the case group had 14 (46.7%) surgeries on the right side and 16 (53.3%) on the left side, compared to 48 (53.3%) on the right side and 42 (46.7%)

on the left side in the control group. There was no significant difference between these proportions ( $p=0.527$ ).

There was no difference in the prevalence of white, brown or black skin color between the groups ( $p=0.200$ ).

There was no statistical difference in the prevalence of type 2 diabetes mellitus between the groups ( $p=0.804$ ). Control group patients had a significantly higher prevalence of SAH ( $p=0.002$ ) and obesity ( $p=0.020$ ), with the remaining comorbidities being assessed as showing no differences (asthma, heart disease and hypothyroidism).

The values obtained from the serum CRP and its variations, as shown in Table 1, did not show any significant difference between the groups.

The CRP<sub>0</sub> level of each patient was considered as the baseline reference level. Serum CRP less than or equal to 5 mg/L was defined as the limit. Normalization of the CRP<sub>21</sub> rate was considered when the value was less than or equal to CRP<sub>0</sub> or less than or equal to 5 mg/L. The variation value of CRP<sub>21</sub> in relation to CRP<sub>0</sub> was measured for those cases that did not normalize. The distribution of frequencies for this classification by group can be seen in Table 2. There was no difference in the normalization of CRP<sub>21</sub> between the groups, with 23.3% in the case group and 24.4% in the control group ( $p=0.902$ ).

The mean age of the case group (62.4 years) was significantly lower than that of the control group (68.8 years) ( $p=0.002$ ). Table 3 shows the age statistics and the normalization index of CRP<sub>21</sub>. The mean BMI of the patients in the case group (28.2kg/m<sup>2</sup>) was significantly lower than in the control group (31.5kg/m<sup>2</sup>) ( $p=0.006$ ). Among obese patients, CRP<sub>0</sub> was significantly higher in the control group.

The CRP values in both sexes did not show any significant difference for CRP<sub>0</sub>, CRP<sub>3</sub>, CRP<sub>21</sub>, or for  $\Delta$ <sub>1</sub>CRP and  $\Delta$ <sub>2</sub>CRP variations between the case and control groups.

SAH is not associated with the CRP value in either group. The normalization rates of CRP<sub>21</sub> between those who had and those who did not have each of the main comorbidities are shown in Table 4.

There was no difference in the rate of postoperative blood transfusion between cases (13.3%) and controls (14.4%) ( $p=1.000$ ) or in the volume transfused ( $p=0.350$ ). Blood transfusion does not influence the values of CRP<sub>0</sub>, CRP<sub>3</sub> and CRP<sub>21</sub> or CRP variations.

Postoperative surgical complications occurred in 5 patients in the case group (16.7%) and 8 patients in the control group (9%) ( $p=0.309$ ). The most frequent complication in the sample was skin necrosis (5%)

**Table 1. Distribution of serum CRP values and their variations by group. Analysis of the values of serum CRP throughout the postoperative period**

Statistic	CRP <sub>0</sub> <sup>4</sup>		CRP <sub>3</sub> <sup>5</sup>		CRP <sub>21</sub> <sup>6</sup>		Δ <sub>1</sub> CRP <sup>7</sup> (%)		Δ <sub>2</sub> CRP <sup>8</sup> (%)	
	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case
Mean	10.1	14.5	102.5	68.5	26.8	25,0	3202,2	1263,5	-46,0	-7,1
Median	5.6	6.3	64.1	51.0	15.8	19,3	892,5	837,0	-72,6	-72,4
SD <sup>1</sup>	12.4	20.9	81.2	70.7	37.2	23,3	5776,7	1241,6	121,1	296,1
CV <sup>2</sup>	1.24	1.44	0.79	1.03	1.39	0,93	1,80	0,98	-2,63	-41,98
p-value <sup>3</sup>	0.730		0.178		0.737		0.636		0.297	

**Legend:** CRP: C-reactive protein.<sup>1</sup> Standard deviation.<sup>2</sup> Coefficient of variation.<sup>3</sup> Student's t test.<sup>4</sup> Serum CRP value the day before surgery.<sup>5</sup> Serum CRP value on the 3rd postoperative day.<sup>6</sup> Serum CRP value on the 21st postoperative day.<sup>7</sup> Percentage of CRP<sub>0</sub> variation that occurred in the first 3 days after surgery.<sup>8</sup> Percentage of CRP<sub>3</sub> variation that occurred between the 3rd and the 21st day after surgery.

**Source:** The authors (2022).

**Table 2. Rate of PCR normalization. Analysis of the values of serum CRP 21 days after the operation, comparing the case and control groups**

Classification	Control	Case
Normalization of the CRP <sub>21</sub> <sup>1</sup>	24.4%	23.3%
CRP <sub>21</sub> <sup>1</sup> up to 10 mg/L above CRP <sub>0</sub> <sup>2</sup>	38.9%	23.3%
CRP <sub>21</sub> <sup>1</sup> from 10 to 20 mg/L above CRP <sub>0</sub> <sup>2</sup>	16.7%	23.3%
CRP <sub>21</sub> <sup>1</sup> from 20 to 50 mg/L above CRP <sub>0</sub> <sup>2</sup>	12.2%	23.3%
CRP <sub>21</sub> <sup>1</sup> from 50 to 100 mg/L above CRP <sub>0</sub> <sup>2</sup>	4.4%	6.7%
CRP <sub>21</sub> <sup>1</sup> with more than 100 mg/L above CRP <sub>0</sub> <sup>2</sup>	3.3%	0%

**Legend:** CRP: C-reactive protein.<sup>1</sup> Serum CRP value on the 21st postoperative day.<sup>2</sup> Serum CRP value the day before surgery.

**Source:** The authors (2022).

**Table 3. Relationship between age and normalization of CRP. Comparative analysis between the study groups between normalization or not of the serum CRP value on the 21st postoperative day and the patient's age, demonstrating that patients with normalized CRP<sub>21</sub> in the case group are significantly younger than patients in the control group**

Variable	Group	CRP <sub>21</sub> <sup>1</sup> non-normalized			CRP <sub>21</sub> <sup>1</sup> normalized			p-value <sup>3</sup>
		Mean	Median	SD <sup>2</sup>	Mean	Median	SD <sup>3</sup>	
Age (years)	Control	69.0	69.0	6.0	68.1	65.5	8.3	0.153
	Case	64.5	68.0	9.1	55.4	59.0	7.7	0.022

**Legend:** CRP: C-reactive protein.<sup>1</sup> Serum CRP value on the 21st postoperative day.<sup>2</sup> Standard deviation.<sup>3</sup> Mann-Whitney test.

**Source:** The authors (2022).

**Table 4. Relationship between the main comorbidities and the normalization of CRP. Comparative analysis between the study groups between the normalization or not of the serum CRP value on the 21st postoperative day and the main comorbidities of the patients in the sample, demonstrating that there was no significant difference**

Comorbidity	Group	CRP <sub>21</sub> <sup>3</sup> normalized without comorbidity (%)	CRP <sub>21</sub> <sup>3</sup> normalized with comorbidity (%)	p-value <sup>4</sup>
SAH <sup>1</sup>	Control	25%	24.3%	1.000*
	Case	35.7%	12.5%	0.204*
Obesity <sup>2</sup>	Control	24.4%	24.5%	0.991
	Case	19%	33.3%	0.640*

**Legend:** CRP: C-reactive protein.<sup>1</sup> Systemic arterial hypertension.<sup>2</sup> Body mass index > = 30kg/m<sup>2</sup>.<sup>3</sup> Serum CRP value on the 21st postoperative day.<sup>4</sup> Chi-square test. \* Fisher's exact test.

**Source:** The authors (2022).

**Table 5. Dosage of corticosteroids used in the case group. Analysis of the corticosteroid values used by patients in the case group over the period evaluated**

Period	Mean	Median	SD <sup>3</sup>	Mínimum	Maximum	CV <sup>4</sup>
Previous use (mg/day)	6	5	6	0	25	1.28
Surgical procedure (mg)	48.77	66.67	30.43	0	125	0.82
D1 <sup>1</sup> (mg)	29.5	20	34.8	0	130	1.36
D2-D3 <sup>1</sup> (mg/day)	14	5	33	0	170	2.72
D4-D21 <sup>1</sup> (mg/day)	6	5	6	0	25	1.28
Total dosage <sup>2</sup> (mg)	212.75	207.5	152.27	25	615.83	0.71

**Legend:** <sup>1</sup> Days after surgical procedure. <sup>2</sup> Total dosage of corticosteroids used by the patient in the period between the collection of CRP<sub>0</sub> and CRP<sub>21</sub>. <sup>3</sup> Standard deviation. <sup>4</sup> Coefficient of variation

**Source:** The authors (2022).

followed by deep vein thrombosis (DVT) with 4 cases (3.3%). There was no difference in the rate of CRP<sub>21</sub> between patients with or without these complications (p=1.000 in cases and p=0.508 in controls).

For 25 of the 30 patients in the case group, corticosteroids were administered during the study period. Table 5 summarizes the dosages administered to these patients in the observed period. For the purpose of standardization, the dosage of different drugs was corrected to prednisolone values, according to pharmacological equivalence.<sup>10</sup> The highest dosages are perioperative and the variability of dosages is high at all times observed. No significant difference was found between

patients in the case group who used or did not use corticosteroids during the study period for the values of CRP<sub>0</sub> (p=0.300), CRP<sub>3</sub> (p=0.666), CRP<sub>21</sub> (p=0.957),  $\Delta_1$ CRP (p=0.251) and  $\Delta_2$ CRP<sub>21</sub> (p=1,000). The normalization rate of CRP<sub>21</sub> was not related to the use of corticosteroids (p=0.565). There was a direct association between the corticosteroid dosage and the CRP<sub>3</sub> value (p=0.002).

## Discussion

CRP is a marker that is difficult to interpret and may be elevated even in the absence of an infection.<sup>11</sup> As a result, our study aimed to identify possible differ-

ences in the serum CRP curve in RA patients undergoing TKA, compared to patients undergoing the same procedure for primary OA. Factors that could influence the curve of serum CRP in the first three weeks after TKA were investigated in both groups. In the present sample, no significant associations were found between the serum CRP curve and age, BMI, sex, blood transfusions or non-infectious postoperative surgical complications. Similar to the present study, Larsson e cols. evaluated the serum CRP curve after elective orthopedic procedures and concluded that these values were not influenced by the type of anesthesia, amount of bleeding, need for blood transfusion, surgical time, drugs administered, age or sex.<sup>12</sup> Laiho e cols. assessed the CRP curve in RA patients undergoing TKA or total hip arthroplasty (THA) and concluded that the presence of RA does not appear to influence the normal response of this biomarker, despite an initial rise.<sup>13</sup> Mäenpää e cols. studied the mean preoperative and postoperative CRP of RA patients undergoing THA or THA review. According to the authors, no significant difference was found between the groups.<sup>14</sup> Maury e cols. demonstrated that CRP has higher values in patients undergoing TKA when compared to THA.<sup>15</sup> After surveying the literature, we did not find articles in Portuguese or English that have assessed serum levels of CRP after TKA in patients with RA.

The patients in the case group were significantly younger than the patients in the control group ( $p=0.002$ ), reinforcing the observation by Abernethy e cols.<sup>2</sup> that patients with knee OA secondary to RA are submitted to TKA earlier than patients with primary OA.<sup>2</sup> Thus, the durability of the procedure should be a concern.

The serum values of CRP and its variations did not show a significant association with the BMI of patients in both groups. The mean BMI of the patients in the case group, however, was significantly lower than the mean BMI of the control group ( $p=0.006$ ). This difference may reflect the influence of obesity on the development of primary OA compared to patients who are not diagnosed with inflammatory arthritis, such as RA. Obesity is a recognized risk factor for the progression of knee OA and arthroplasty infection.<sup>16</sup> In addition, it is considered a systemic inflammatory state and higher reference values for serum CRP for obese patients have already been proposed.<sup>17</sup> This statement corroborates the findings of the present study, in which the CRP[0 dosage was significantly higher in the control group, when comparing obese and non-obese patients.

The incidence of surgical complications was low, with no statistical difference between the groups. Skin necrosis was the most frequent complication, affecting 3.3% of patients in the case group and 5.5% of patients in the control group. DVT was diagnosed in 6.7% of patients with RA and in 2.2% of patients with primary OA. Ravi e cols. compared the incidence of postoperative surgical complications in patients undergoing arthroplasty by RA and primary OA. According to the researchers, there is no difference in the incidence of DVT between the groups.<sup>18</sup>

Some patients in the case group used continuous corticosteroids as part of RA treatment. Different doses of medication were used in these patients during the study period. Although the use of medication did not present a significant difference in the serum values of CRP and its variations, in the comparison between the patients in the case group who used and did not use corticosteroids in the studied period, a direct correlation was found between the corticosteroid dosage and the value serum CRP in the first three days after surgery. This association may be related to the severity of the disease and the inflammatory process and, consequently, the dosage of the control medication. This fact is supported by the cases described by Mysler e cols., who demonstrated that patients with RA who make chronic use of prednisolone higher than 5mg/day have significantly higher baseline serum CRP values than patients using lower doses.<sup>19</sup> Laiho e cols. found no significant difference in RA patients undergoing arthroplasty in the group with or without the use of corticosteroids.<sup>20</sup> As a result, they claim that CRP generally decreases in patients with RA using low-dose corticosteroids. There were no statistically significant differences between groups in the comparison of serum CRP values or CRP variations during the period evaluated.

However, the mean CRP values among patients with RA was 14.5mg/L and only 14 out of 30 patients (46.47%) had a serum CRP value considered normal (up to 5 mg/L). Among the patients in the control group, 41 of the 90 patients (45.55%) had a serum CRP below 5mg/L on the eve of surgery, with an average of 10.1 mg/L. The findings suggest a tendency to present higher baseline levels for patients with RA compared to patients with primary OA. These results are compatible with findings described in the literature in the assessment of serum CRP levels in these patients.<sup>8,9</sup>

Only 23.3% of patients with RA and 24.4% of patients with primary OA undergoing TKA had normalized values for serum CRP 3 weeks after the

procedure, with no statistical difference between the groups. Laiho e cols. evaluated the serum CRP curve in RA patients undergoing knee and hip arthroplasties and considered that the serum CRP values reverted to preoperative standards in approximately 1 week, despite presenting high values at that time, with a median of 18 mg/L and range from 5 to 110 mg/L, similar to the values in our sample.<sup>13</sup> Barretto e cols. evaluated the serum CRP curve of patients with primary OA undergoing TKA and

found a normal CRP normalization rate of only 28.2% 3 weeks after the surgical procedure.

## Conclusion

The serum values of C-reactive protein after TKA do not differ between patients with primary osteoarthritis or secondary to RA. Thus, the reference values can be considered equal in both cases.

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