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Original article

Evaluation of serum levels of C-reactive protein after total knee arthroplasty☆

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ABSTRACT

Objective: To evaluate the behavior of C-reactive protein (CRP) levels in the first three weeks after total knee arthroplasty (TKA) and define the factors related to its variation.
Methods: We evaluated the CRP values in 103 patients undergoing primary TKA. Serum CRP was measured on the day before surgery, and on the third and twenty-first days after the procedure.
Results: PCR showed sudden increase on the third day after surgery, reaching the mean value of 111.9 mg/L, median 75.9 mg/L. Only one-third of the patients returned to normal levels in the third week. In the immediate postoperative period, CRP was not correlated with body mass index (BMI), age, gender, blood transfusion, or complications.
Conclusion: Serum CRP remains high in the third week after TKA in most patients, and this change is primarily related to surgical trauma.

Avaliação dos níveis séricos da proteína C-reativa após artroplastia total do joelho

Palavras-chave:
Proteína C-reativa
PCR
Joelho
Osteoartrite
Artroplastia

RESUMO

Objetivo: Avaliar o comportamento da proteína C-reativa (PCR) sérica nas três primeiras semanas após artroplastia total do joelho (ATJ) e definir os fatores relacionados a sua variação.
Métodos: Foram avaliados os valores da PCR em 103 pacientes submetidos à ATJ primária. A PCR sérica foi dosada na véspera da cirurgia, no terceiro e no 21° dia após o procedimento.
Resultados: A PCR apresentou elevação súbita no terceiro dia após a cirurgia, atingiu o valor médio de 111.9 mg/L, com mediana de 75,9 mg/L. Somente um terço dos pacientes

☆ Study conducted at the Instituto Nacional de Traumatologia e Ortopedia (Into), Centro de Cirurgia do Joelho, Rio de Janeiro, RJ, Brazil.

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apresentou normalização na terceira semana. No pós-operatório imediato, não foi encontrada correlação da PCR com índice de massa corporal (IMC), idade, gênero, hemotransfusão ou complicações dos pacientes.

Conclusão: A PCR sérica permanece elevada na terceira semana após ATJ na maioria dos pacientes e essa alteração está relacionada essencialmente ao trauma cirúrgico.

Introduction

Osteoarthritis (OA) is the leading cause of musculoskeletal disability worldwide,[1] and the main physical limitation factor in the elderly population.[2] This serious public health problem affects approximately 12.4 million Brazilians.[3] Due to anatomical and biomechanical factors, the most commonly affected joint is the knee.[1]

The increased life expectancy and desire for greater activity have exponentially increased the demand for total knee arthroplasty (TKA).[4] It represents one of the most successful orthopedic procedures of the century. Despite the success of TKA, post-operative infection remains a devastating complication.[5] Early diagnosis is difficult, as the signs of physical examination and serological markers can present alterations due to surgical trauma.[6]

C-reactive protein (CRP) is an example of an acute-phase protein. It is synthesized mainly by the hepatocyte, and its function is to activate the complement system through the classical pathway.[7] After infectious or inflammatory stimuli, serum CRP levels may rise abruptly, reaching up to 1000 times the baseline value in 48 h.[8]

This substance has been used in clinical practice for over 70 years as a marker of infection and/or inflammation, but its serum values and its response to stimuli vary widely, and the factors associated with this oscillation are still little known.[7]

The evaluation of serum CRP forms a part of the propedeutics for the diagnosis of periprosthetic infection.[9] The test has high sensitivity and low specificity,[10] and may be influenced by factors such as age, gender, comorbidities,[9] and body mass index,[11] in addition to the surgical trauma.

This study aimed to assess the behavior of serum CRP in the first three weeks after TKA and to establish the factors related to its variation.

Material and methods

After approval of the project by the Institution Review Board, under number 804.216, serum CRP was measured prospectively and for convenience in 103 patients submitted to primary TKA between September 2014 and March 2015.

The study included all patients who underwent primary TKA and accepted to participate by signing an informed consent form. Patients undergoing revision arthroplasty and those with inflammatory diseases were excluded.

On the day before surgery, the first sample of 2 mL of venous blood was collected to determine the preoperative quantitative CRP (CRP_0); assessment was made in the laboratory of the institution. The biochemistry analyzer BT3000 Plus® (Wiener Lab, Rosario, Santa Fe, Argentina) was used for the analysis with the turbidimetric method, whose reference values in adults is 5 mg/L for infectious diseases. Patients had their stature and body weight measured. Weight was documented in kilograms and height in meters. These data were used to calculate the body mass index (BMI) of each patient in order to categorize them according to the parameters of the World Health Organization (WHO).[12]

The same implant was used in all cases (PFC Sigma® DePuy Synthes) and the posteriorly stabilized model with patellar replacement was chosen. Intramedullary guides were used for the femoral cut and extramedullary guides for the tibial cut. Patients were operated with the use of perioperative ischemia; the cuff was applied at the thigh level, with a pressure 100 mm/Hg above the systolic pressure.

Pre-anesthetic assessment, filed in the medical record, was used to document the underlying pathologies and the clinical status of the patients.

On the third day after the arthroplasty, while patients were still hospitalized, blood collection procedure for serum CRP was repeated (CRP_3).

Patients were discharged according to clinical criteria, and an outpatient follow-up appointment was scheduled for the 21st day after surgery. At the follow-up appointment, before consultation or any manipulation of the surgical wound, a blood sample was collected for the third CRP measurement (CRP_{21}).

A spreadsheet containing patients' initials, medical record number, age, gender, skin color, primary knee pathology, laterality, clinical comorbidities, body weight and height, BMI, and CRP_0, CRP_3, and CRP_{21} values was created.

From the data collected, two files were created and then analyzed using SPSS (Statistical Package for the Social Sciences), version 22.0, and Microsoft Excel 2007.

Descriptive analysis was presented as tables of the observed data, expressed as mean, standard deviation, median, and minimum and maximum for numerical data, and frequency (n) and percentage (%) for categorical data, as well as illustrative graphs. CRP_{21} was considered normalized when it reached a value lower than or equal to 5 mg/L or lower than or equal to CRP_0.

In the inferential analysis, to verify the association between qualitative variables, chi-squared test was used; when inconclusive, Fisher's exact test was applied. For quantitative variables, the normality hypothesis was verified by the Kolmogorov–Smirnov and Shapiro–Wilk tests. When distribution was normal, comparison between the two groups was made by Student's t-test, otherwise, the nonparametric

Table 1 – Sample characterization.

Variable	Number	Percentage
Gender		
Male	24	23.3
Female	79	76.7
Laterality		
Right	60	58.3
Left	43	41.7
Ethnicity		
White	35	34
Mixed-race	51	49.5
Black	17	16.5

Source: Data from the institution medical records.

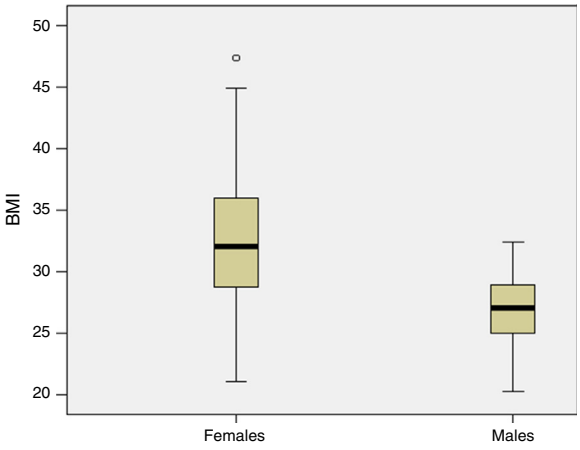

Fig. 1 – Body mass index (BMI) distribution according to gender.

Mann–Whitney test was used. Comparison between more than two independent groups was conducted using the Kruskal–Wallis test. The quantitative variables were analyzed by two approaches: by calculating Pearson's linear correlation coefficient for normal distributions and Spearman's correlation coefficient for non-normal. A 5% significance level was adopted for rejecting the null hypothesis.

Results

The study included 103 knees of 117 patients who underwent primary TKA; 24 patients were male and 79 were female. Table 1 presents the distribution of the sample regarding sex, operated side, and ethnicity.

Mean age of patients was 68.9 years (±6.4), ranging from 55 to 91. Mean age of female patients was 69 years (±6.3) and male patients, 68.3 (±6.9). The Mann–Whitney test indicated that both groups were similar regarding age ($p = 0.910$). There was no association between age and CRP_0 ($p = 0.688$), CRP_3 ($p = 0.455$), and CRP_{21} ($p = 0.831$).

Patients had a mean BMI of 31.4 (±5.8); 32.7 (±5.8) for females and 27 (±3.2) for males. Student's *t*-test showed that BMI was significantly higher in the female group than in the male group ($p = 0.000$). This difference is shown in Fig. 1.

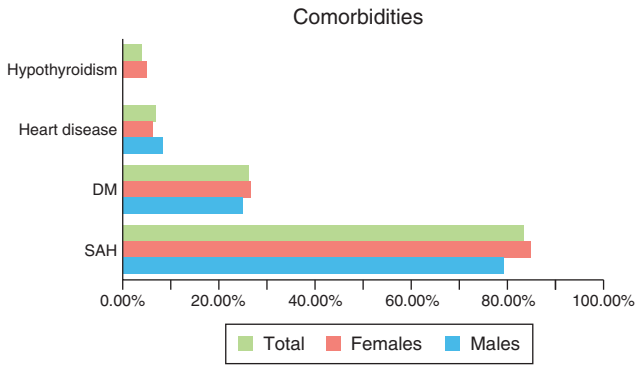

Fig. 2 – Incidence of comorbidities. DM, diabetes mellitus; SAH, systemic hypertension.
***Source*: Data from the institution.**

Only 15.3% of the patients were eutrophic. Remaining of the sample was overweight (31.6%) or obese (53.1%). The CRP_{21} normalization rate was not correlated with BMI ($p = 0.516$).

All patients had gonarthrosis in the operated knee; 100 had primary gonarthrosis and three had secondary gonarthrosis. Only 10.7% of the patients did not present a systemic pathology. Among the 89.3% of patients with comorbidities, systemic arterial hypertension (SAH) was the most prevalent, followed by diabetes mellitus (DM), heart disease, and hypothyroidism. The distribution of the most frequent clinical comorbidities, divided by gender and total sample, is shown in Fig. 2.

Postoperative complications occurred in ten cases (9.7%), comprising nine female patients (11.4%) and one male (4.2%). Skin necrosis was the most frequent complication, observed in six patients, followed by deep vein thrombosis (DVT; three cases) and postoperative rigidity (one case); 14 patients (13.6%) received postoperative blood transfusion, all red cell concentrates (RCC).

The CRP values were submitted to the Shapiro–Wilk normality test; the null hypothesis was rejected ($p = 0.000$) and a non-Gaussian distribution was demonstrated. Table 2 presents these values in the total sample and their statistical variables.

The rate of CRP normalization by the third week was 28.2% in the total sample; 26.6% in females and 33.3% in males. There was no significant difference between genders ($p = 0.520$).

Table 3 presents the rate of normalization after the third week in the total sample and divided by gender.

The evolution of the mean serum CRP from the preoperative period to the 21st day is shown in Fig. 3.

The rate of CRP_{21} normalization was not correlated with BMI ($p = 0.516$) or patient's age ($p = 0.831$). The group that received blood transfusion presented normalization in 14.3% of the cases. Among those who did not receive transfusion, this rate reached 30.3%. Despite the discrepancy, Fisher's exact test showed no statistically significant difference between the two groups ($p = 0.339$).

The rate of CRP_{21} normalization for patients with postoperative complications was 40%. In the group that did not present complications, this rate was 26.9%. This difference was not statistically significant ($p = 0.462$).

Table 2 – C-reactive protein (CRP) values.

Statistics	CRP_0 (mg/L)	CRP_3 (mg/L)	CRP_{21} (mg/L)	Δ_1CRP (%)	Δ_2CRP (%)
Mean	15.1	111.9	27.4	3118.6	−47.5
95% CI	10.5 19.6	94.2 129.6	20.1 34.6	2048.2 4189.0	−70.4 −24.6
Median	6.4	75.9	15.4	1051.9	−73.6
Standard deviation	23.2	90.4	36.9	5476.9	117.1
Minimum	0.6	4.8	0.7	−62.8	−99.1
Maximum	132.5	384.0	263.9	25,242.5	962.5
Raw variation	131.9	379.2	263.2	25,305.3	1061.6
Correlation coefficient	1.5	0.8	1.4	1.8	−2.5

Δ_1CRP, variation between CRP_0 and CRP_3; Δ_2CRP, variation between CRP_3 and CRP_{21}.

Table 3 – Rate of C-reactive protein (CRP) normalization.

Classification	Gender		Total
	Female	Male	
CRP_{21} was normalized	21	8	29
	26.6%	33.3%	28.2%
CRP_{21} up to 10 mg/L > CRP_0	29	7	36
	36.7%	29.2%	35.0%
CRP_{21} from 10 to 20 mg/L > CRP_0	14	3	17
	17.7%	12.5%	16.5%
CRP_{21} from 20 to 50 mg/L > CRP_0	8	4	12
	10.1%	16.7%	11.7%
CRP_{21} from 50 to 100 mg/L > CRP_0	4	1	5
	5.1%	4.2%	4.9%
CRP_{21} more than 100 mg/L > CRP_0	3	1	4
	3.8%	4.2%	3.9%
Total	79	24	103
	100%	100%	100%

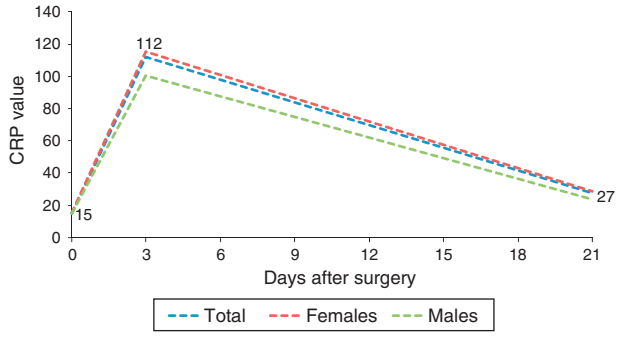

Fig. 3 – Variation of the mean C-reactive protein (CRP) from the preoperative assessment to the 21st day.

Discussion

CRP is an acute-phase protein that has been used as inflammatory or infection marker since 1930. In the last decade, it has received special attention due to its predictive role in several diseases.[1] It has an important role in orthopedics, being used in the diagnosis and control of infections.[13]

With the increase in life expectancy and the growth of obesity, the rates of OA have increased exponentially, since these factors are directly linked to the genesis of the disease.[14] TKA promotes an effective relief of pain and improves function.[15] Projections suggest that approximately 3.5 million knee arthroplasties will be performed in the United States in 2030.[16] Despite being a safe surgery, infection is a potentially devastating complication, ranging between 0.4% and 2% of patients.[17] Diagnosis in the acute phase allows treatment with debridement, implant retention, and antibiotic therapy;[1] the success rates can be as high as 36%,[18] as long as the treatment is initiated before the third week.[1]

The work up of periprosthetic infections is based on clinical and laboratory findings.[13] The early identification of this complication is difficult because the signs of the physical examination are not reliable and serological markers are elevated in the immediate postoperative period.[6] CRP can be a useful tool; it presents high sensitivity, but low specificity.[10] Understanding CRP behavior in the immediate postoperative period is critical to increasing the reliability of the use of this marker for diagnosis.

The rate of CRP normalization after the third postoperative week was 28.2%; 26.6% among women and 33.3% among men. The sample presented a ratio of 3.29 females for every male, which is consistent with the literature.[4,19] No differences were observed in CRP variation regarding gender ($p = 0.520$), although Kraus et al.[20] and Choi et al.[21] have demonstrated significantly higher values in women.

Mean age was 68.9 years (±6.4), reaching patients in the seventh decade of life. The incidence of gonarthrosis increases with aging, reaching 49.7% of people over 65 years.[19] CRP's behavior in the acute postoperative period showed no correlation with age, although Parvizi et al.[9] and Choi et al.[21] reported that this influence could occur.

Most patients were overweight or obese, which confirms the role of obesity in the genesis[14] and progression of OA.[22] The adipose tissue produces inflammatory agents, including CRP. Excess body fat perpetuates a subclinical inflammatory state that may raise the baseline CRP levels in this group.[23] No differences in the rate of CRP_{21} normalization were observed between obese and nonobese patients ($p = 0.704$). However, the present sample consisted of only 15.3% normotrophic patients, which hindered this comparison. Liu et al.[11] analyzed the CRP values of 1571 patients undergoing TKA revision and divided them into four groups for the presence of infection and obesity. They found no difference in the CRP value between obese and non-obese patients ($p = 0.23$); nonetheless, these authors suggest that increasing the cutoff point for obese patients would increase the specificity of this test for the diagnosis of infection. Choi et al.[21] found a direct relationship between BMI and CRP, but stronger in female patients.

The incidence of comorbidities in the sample was consistent with the distribution in the population at the same age range[24] and was not associated with the rate of CRP_{21} normalization ($p = 0.739$).

Complications were observed in 9.7% of patients, and there was no direct relationship with the rate of CRP_{21} normalization ($p = 0.462$). No patient presented infectious complications, which may have influenced the absence of relation. The rate of blood transfusion in the present sample was in agreement with national literature[25] and did not influence the CRP curve in the acute phase.

The present study revealed two important findings: the variation of CRP in the immediate postoperative period (CRP_3), which reached the mean value of 111.9 mg/L (CRP_0), and the rate of normalization after the third week (CRP_{21}), which is expected in only one-third of patients. This rapid increase in CRP_3 after tissue injury demonstrates the participation of this protein in the host's defense system. Regardless of the normalization, a further increase in CRP after the first week is suggestive of infection.[26] Since there were no cases of infection in the present sample, this increase was due exclusively to tissue damage.

Shen et al.[26] suggest that CRP levels after arthroplasty are directly linked to the region and extent of surgical trauma, regardless of blood transfusion, age, or sex of the patient, which is consistent with the present findings. Thienpont et al.[27] found no difference in the CRP values after conventional or minimally invasive TKA and demonstrated that the elevation of the protein is related to bone marrow trauma.

Conclusion

The value of serum CRP shows a sudden increase on the third day after total knee arthroplasty. Two-thirds of patients remain with elevated CRP in the third week after surgery, and this change is essentially related to surgical trauma.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Scott WN. Insaal & Scott surgery of the knee. 5th ed. Philadelphia: Elsevier/Churchill Livingstone; 2012.
2. Centers for Disease Control and Prevention (CDC). Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation. United States, 2007–2009. Morb Mortal Wkly Rep. 2010;59(39):1261–5.
3. Coimbra IB, Rezende MU, Plaper PG. Osteoartite (artrose) – Cenário atual e tendências no Brasil. São Paulo: Limay; 2012.
4. Loures FB, Góes RFA, Palma IM, Labronici PJ, Granjeiro JM, Olej B. Anthropometric study of the knee and its correlation with the size of three implants available for arthroplasty. Rev Bras Ortop. 2016;51(3):282–9.
5. Sharkey PF, Lichstein PM, Shen C, Tokarski AT, Parvizi J. Why are total knee arthroplasties failing today – has anything changed after 10 years? J Arthroplasty. 2014;29(9):1774–8.
6. Yi PH, Cross MB, Moric M, Sporer SM, Berger RA, Della Valle CJ. The 2013 Frank Stinchfield Award: diagnosis of infection in the early postoperative period after total hip arthroplasty. Clin Orthop Relat Res. 2014;472(2):424–9.
7. Ablij H, Meinders A. C-reactive protein: history and revival. Eur J Intern Med. 2002;13(7):412.
8. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999;340(6): 448–54.
9. Parvizi J, Zmistowski B, Berbari EF, Bauer TW, Springer BD, Della Valle CJ, et al. New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. Clin Orthop Relat Res. 2011;469(11):2992–4.
10. Jacovides CL, Parvizi J, Adeli B, Jung KA. Molecular markers for diagnosis of periprosthetic joint infection. J Arthroplasty. 2011;26 6 Suppl, 99-103.e1.
11. Liu JZ, Saleh A, Klika AK, Barsoum WK, Higuera CA. Serum inflammatory markers for periprosthetic knee infection in obese versus non-obese patients. J Arthroplasty. 2014;29(10):1880–3.
12. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894, i-xii, 1-253.
13. Parvizi J, Gehrke T. Consenso internacional em infecções articulares periprotéticas. Accessed in 18/01/2016. Available in: http://www.rbo.org.br/pdf/consensos/consensos_ciiap.pdf.
14. Felson DT. The epidemiology of knee osteoarthritis: results from the Framingham osteoarthritis study. Semin Arthritis Rheum. 1990;20 3 Suppl. 1:42–50.
15. Cheng CK, Lung CY, Lee YM, Huang CH. A new approach of designing the tibial baseplate of total knee prostheses. Clin Biomech (Bristol, Avon). 1999;14(2):112–7.
16. Kurtz SM, Lau E, Ong K, Zhao K, Kelly M, Bozic KJ. Future young patient demand for primary and revision joint replacement: national projections from 2010 to 2030. Clin Orthop Relat Res. 2009;467(10):2606–12.
17. Carvalho Júnior LH, Temponi EF, Badet R. Infection after total knee replacement: diagnosis and treatment. Rev Bras Ortop. 2013;48(5):389–96.
18. Odum SM, Fehring TK, Lombardi AV, Zmistowski BM, Brown NM, Luna JT, et al. Irrigation and debridement for periprosthetic infections: does the organism matter? J Arthroplasty. 2011;26 6 Suppl.:114–8.
19. Centers for Disease Control and Prevention (CDC). Arthritis: National Statistics. Accessed in 20/01/2016. Available in: http://www.cdc.gov/arthritis/data_statistics/national-statistics.html.
20. Kraus VB, Stabler TV, Luta G, Renner JB, Dragomir AD, Jordan JM. Interpretation of serum C-reactive protein (CRP) levels for cardiovascular disease risk is complicated by race, pulmonary

disease, body mass index, gender, and osteoarthritis. Osteoarthritis Cartilage. 2007;15(8):966–71.
21. Choi J, Joseph L, Pilote L. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. Obes Rev. 2013;14(3):232–44.
22. Loures FB, Góes RFA, Labronici PJ, Barreto JM, Olej B. Avaliação do índice de massa corporal como fator prognóstico na osteoartrose do joelho. Rev Bras Ortop. 2016;51(4):400–4.
23. Nazmi A, Oliveira IO, Gonzales DA, Gigante DP, Horta BL, Victora CG. Differential and cumulative impact of BMI and central obesity on C-reactive protein levels: findings from a Brazilian birth cohort. Am J Epidemiol. 2009;169 Suppl.11:S83.
24. Souza ARA, Costa A, Nakamura D, Mocheti LN, Stevanato Filho PR, Ovando LA. Um estudo sobre hipertensa˜o arterial sistêmica na cidade de Campo Grande, MS. Arq Bras Cardiol. 2007;88(4):441–6.
25. Cardozo RT, Souza Júnior EF, Alves WC, Barbi Filho F. Artroplastia total do joelho: indicação de transfusão sanguínea de acordo com a variação hematimétrica e os sintomas clínicos de hipoperfusa˜o. Rev Bras Ortop. 2014;49(5):507–12.
26. Shen H, Zhang N, Zhang X, Ji W. C-reactive protein levels after 4 types of arthroplasty. Acta Orthop. 2009;80(3):330–3.
27. Thienpont E, Grosu I, Jonckheere S, Yomi JC. C-reactive protein (CRP) in different types of minimally invasive knee arthroplasty. Knee Surg Sports Traumatol Arthrosc. 2013;21(11):2603–10.