Characterizing the Acute Phase Response in Healthy Patients Following Total Joint Arthroplasty: Predictable and Consistent

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Abstract

Background: During surgery, trauma to musculoskeletal tissue induces a systemic reaction known as the acute phase response (APR). When excessive or prolonged, the APR has been implicated as an underlying cause of surgical complications. The purpose of this study was to determine the typical APR following total joint arthroplasty in a healthy population defined by the Charlson Comorbidity Index (CCI).

Methods: This retrospective study identified 180 healthy patients (CCI < 2) who underwent total joint arthroplasty by a single surgeon for primary osteoarthritis from 2013 to 2015. Serial measurements of C-reactive protein (CRP) and fibrinogen were obtained preoperative, perioperative, and at 2 and 6 weeks postoperative.

Results: Postoperative CRP peaked during the inpatient period and returned to baseline by 2 weeks. Fibrinogen peaked after CRP and returned to baseline by 6 weeks. Elevated preoperative CRP correlated with a more robust postoperative APR for both total hip arthroplasty and total knee arthroplasty, suggesting that a patient's preoperative inflammatory state correlates with the magnitude of the postoperative APR.

Conclusion: Measurement of preoperative acute phase reactants may provide an objective means to predict a patient's risk of postoperative dysregulation of the APR and complications.

The acute phase response (APR) is a systemic reaction to tissue injury; it is mediated by the liver and characterized by the modulation of more than 1000 genes. This response results in the production of cytokines that prevent hemorrhage, combat infection, and stimulate wound

healing. Although the APR is essential for normal coagulation and immunity, dysregulation leads to complications such as life-threatening hemorrhage, poor wound healing, and venous thromboembolism [1]. These thromboembolic complications stem from Virchow's triad of venous stasis, endothelial injury, and hypercoagulability. Prior studies have demonstrated that the magnitude and duration of this response directly correlates with the level of initial tissue injury and predicts poor outcomes in injured patients [2–4].

Surgical trauma during total joint arthroplasty (TJA) evokes a profound APR [5–7]. Prior studies have shown that C-reactive protein (CRP), an acute phase reactant, and erythrocyte sedimentation rate (ESR), an indirect marker of the APR, follow general trends post-TJA [5–7]. Yet, these early studies from the 1990s were conducted under different conditions than current standards of practice and have high variability for maximum inpatient values and time to resolution for CRP and ESR [6,8]. Moreover, this variability is also seen in a recent study by Yombi et al [9] following conventional and minimally invasive total knee arthroplasty (TKA). These studies did not address the APR in the context of an objectively defined healthy population and a large sample size [6,8,9]. Therefore, this study aims at measuring the APR following arthroplasty in a healthy population with current implants, techniques, and standards of practice. Furthermore, this investigation proposes to use fibrinogen to study the APR rather than ESR. ESR quantifies inflammation through an indirect measurement of fibrinogen [10,11], an acute phase reactant that is upregulated following injury [12]. Prior investigations showed that ESR does not return to normal within 1 year following TJA [6]. This imprecision has lead others to conclude that while ESR advanced medical science when introduced in the 1920s, it is often misleading because it is greatly influenced by immunoglobulins, plasma constituents, and changes to erythrocyte morphology and number [13]. Thus, ESR is a less-sensitive marker for the APR than fibrinogen, an acute phase reactant.

This study aims at describing the typical APR exhibited by healthy patients following uncomplicated TJA with current surgical techniques through serial measurement of CRP and fibrinogen. The authors hypothesize that the APR following uncomplicated primary TJA in healthy patients is both consistent and predictable.

Methods

Sample Population and Inclusion Criteria

This IRB-approved retrospective cohort study (level of evidence III) was conducted on patients undergoing primary total hip arthroplasty (THA) and primary TKA at Vanderbilt University Medical Center from 2013 to 2015; 207 patients were enrolled in the study; 180 patients met both the inclusion and exclusion criteria. Adult patients aged between 17 and 88 years with a Charlson Comorbidity Index (CCI) <2 were included in the study. The CCI is a widely accepted and tested method for predicting the influence of comorbidities on functional outcomes [14], implant survival [15], length of stay [16,17], and mortality [18]. The score ranges from 0 to 33 with an increasing score indicating the presence of multiple comorbidities [19]. The CCI was calculated for each patient through review of comorbidities in the electronic medical records.

Surgical Approach and Exclusion Criteria

All surgeries included in the study were performed by a single surgeon (G.G.P.). The surgeon used a posterior surgical approach for the THA and a medial parapatellar arthrotomy with tourniquet use for the TKA. All patients in the study were placed on Celebrex during the perioperative period unless contraindicated. Contraindications included known hypersensitivity to celecoxib, sulfon-amides, aspirin, or other nonsteroidal anti-inflammatory drugs as well as patients with a history of gastrointestinal sensitivity or peptic ulcer disease. Atypical or complex primary arthroplasty procedures for postinfectious arthrosis, posttraumatic osteoarthritis, or arthroplasty were excluded from the study. Patients requiring THA or TKA revision were also excluded. The electronic medical record, containing both office and hospital records, was reviewed for complications in the 6-week postoperative period.

Laboratory Methods

CRP and fibrinogen laboratory values were collected at preoperative, perioperative, and postoperative 2-week and 6-week time points as part of regular standard of care for tracking acute inflammation. Laboratory tests were drawn on the floor and processed by our institution's clinical laboratory, which is Clinical Laboratory Improvement Amendments (CLIA) certified, accredited by the College of American Pathologists, and licensed by the state of Tennessee. Fibrinogen was tested in accordance with the Clauss clotting method using the STA-R Evolution Analyzer with reagents from Diagnostica Stago, Inc. Interassay coefficients of variation have been reported to range from 3.0% to 4.8% [20]. CRP levels were measured using an immunoturbidimetric assay with the Architect C1600 by Abbott Laboratories with reported interassay coefficients of variation of 0.44% to 1.25% [21].

Temporal Criteria for Laboratory Values

The preoperative period was defined as 40 days before surgery; perioperative period was defined as the end of surgery to discharge; week 2 was defined as postoperative day 10 to 20; and week 6 was defined as postoperative day 35 to day 50. The wide time intervals for postoperative laboratory values were secondary to variability in clinic scheduling. Laboratory values not taken during these time frames were excluded from analysis. Percent resolution of max for CRP and fibrinogen was defined as the change from maximum at 2 and 6 weeks divided by the maximum change from baseline.

Statistical Analysis

Mann-Whitney 2-tailed unpaired t tests were performed to compare the non-Gaussian THA and TKA cohorts. Unpaired t tests using the Holm-Sidak method were performed to compare the 25th and 75th percentile CRP and fibrinogen values of the patient cohorts and to compare the THA and TKA APR time courses.

Estimates of sample size were calculated based on the evaluation of peak CRP and fibrinogen following TKA and THA. For a study of alpha 0.05 and 1-beta 0.80, 13 patients were required for each group based on a difference in population means of 49.7 mg/L and standard deviation of difference of 59.25 mg/L for CRP. This was consistent with prior studies [8]. For fibrinogen with alpha = 0.05 and 1-beta = 0.80, 54 patients were required for

each group based on a difference in population means of 42.5 mg/dL and standard deviation of difference of 109.8 mg/dL. This study was adequately powered with 118 TKA and 62 THA patients.

Determination of Consistency and Predictability

To test the hypothesis that the APR is consistent and predictable, these terms must first be established. Consistency is defined as the ability to significantly distinguish between the THA and TKA cohorts with respect to inpatient maximum value and time to inpatient maximum. Predictability is defined as the ability for preoperative acute phase reactants to predict the postoperative APR. This will be tested by a subset analysis of the THA and TKA cohorts in the 25th and 75th quartiles for preoperative CRP values. If there is a significant difference between the quartiles for postoperative CRP and fibrinogen, then the null hypothesis will be rejected.

Results

The sample demographics for the study cohort are reported in Table 1. The sample population had few comorbidities, with a median CCI of 0 with the 25th and 75th interquartile range of 0–1 for both TKAs and THAs. There were no complications recorded in either of the populations for 6 weeks postoperatively.

The Acute Phase Response Was Consistent for THA and TKA Cohorts

The CRP and fibrinogen responses to TJA were consistent for both TKA and THA. In both procedures, postoperative CRP and fibrinogen peaked during the perioperative period and returned to baseline at 2 and 6 weeks, respectively (Fig. 1). The peak CRP for TKA and THA was 184.3 mg/L and 134.6 mg/L, respectively. The peak CRP was significantly higher for TKA than THA ($P < .0001$). The peak fibrinogen for TKA and THA was 608.1 mg/dL and 565.6 mg/dL ($P .010$), respectively.

CRP has a narrow peak (in comparison to fibrinogen) around postoperative day 2 with 93%–95% resolution by week 2 (Table 2). Fibrinogen has a broad peak (with respect to CRP), as indicated by the wide interquartile range for time to max, and has 87%–96% resolution by week 6.

The Acute Phase Response Was Predictable for THA and TKA Cohorts

An elevated preoperative APR correlated with higher post-operative acute phase reactant measurements. For patients undergoing THA, postoperative fibrinogen and CRP were higher for patients with preoperative CRP in the 75th percentile compared to those in the 25th percentile at each time point (Fig. 2). This was also true for TKA for all measurements except the fibrinogen 2-week time point (Fig. 3).

Discussion

This study demonstrates that the APR following THA and TKA is both predictable and consistent in healthy patients operated on by a single surgeon. Furthermore, there is a different response to TKA and THA (Fig. 4A). We hypothesize that the elevated APR in

patients undergoing TKA might be attributed to the use of a tourniquet and the involvement of an additional long bone when compared to the APR for THA. Interestingly, the results of this study demonstrate that an elevated preoperative APR predisposes patients to a more robust postoperative APR.

Knowledge of how the APR resolves may be useful in guiding postoperative thromboprophylaxis. The 3 aspects of Virchow's triad, tissue injury, hypercoagulability, and stasis exist in the perioperative period following TJA. CRP and fibrinogen represent 2 components of the triad, namely tissue injury [22] and hypercoagulability [23], respectively (Fig. 4B). In this study, CRP and fibrinogen return to their preoperative baselines by 2 and 6 weeks, respectively, with the difference in time to resolution due to their relative half-lives. Therefore, it would appear that the tissue injury aspect of Virchow's triad resolves 2 weeks postoperatively. Given that the third aspect of Virchow's triad, stasis, ends with early mobilization and ambulation within the hospitalization period [24–26], two-thirds of the triad have returned to baseline at 2 weeks. Therefore, we hypothesize that in a healthy population, discontinuation of thromboprophylaxis theoretically may be indicated by 2 weeks postoperation.

In comparison with prior investigations [5,6,8,9], this study attempted to limit variability in outcomes through selection of patients who underwent TJA by a single high-volume joint replacement specialist, thereby providing consistent surgical trauma and better standardization of postoperative care. In addition, the study population included only healthy patients objectively defined by a CCI < 2. The CCI has been validated to predict comorbidity and complications in many fields, including TJA [27–31]. Moreover, the exclusion of patients with multiple comorbidities markedly reduced the distribution and spread of maximum inpatient laboratory values of CRP in comparison to the studies of White et al and Yombi et al. Although our study includes a highly specific patient cohort, the consistency of median laboratory values with prior studies that include different patient populations and surgical techniques (Table 3) suggests that the results are generalizable to a broader population [5,7–9]. This was not true with all prior studies; most notably, our study had a 29.2% and 41.9% reduction in maximum CRP for TKA and THA, respectively, in comparison with the results of Bilgen et al [6], conducted with a limited cohort in Turkey during the late 90s. In general, the authors note that despite surgical advances, our data in the context of prior studies suggest that the APR to both TKA and THA does not vary significantly and that differences in surgical technique have a minimal effect on the APR following TJA. This conclusion is consistent with Yombi et al's investigation of the time course of CRP following minimally invasive and conventional TKA, in which the study found no difference in inpatient CRP between the 2 surgical approaches.

This study was limited in its ability to determine the precise time-to-maximum value for the acute phase reactants measured due to intermittent monitoring. The same limitation prevented precise measurement of the time to resolution for CRP and fibrinogen, as levels were only recorded at 2-week and 6-week post-operative follow-up visits. While the strength of this study was in the objective exclusion of multiple comorbidities with a CCI < 2, the authors believe that the inclusion of a wider range of pathologies would have allowed for the expansion of the interquartile comparisons of preoperative acute phase reactants.

Additionally, this study is somewhat limited by its relatively small sample size as only 180 patients were enrolled and these patients were split between 2 cohorts. Previous studies describing the APR to TKA and THA have similarly small samples, so a future large multi-institutional study would be helpful in validating these findings among a broader population.

Overall, the APRs to TKA and THA are predictable and reproducible in healthy patients. Knowledge of the normal APR to TJA in healthy patients helps identify patients with pathologic deviations from the trend. In this study's cohort of patients, an elevated preoperative CRP predicted an increase in postoperative CRP and fibrinogen. No prior study has reported the relationship between preoperative CRP and postoperative acute phase reactants following TJA. These data suggest that an elevated preoperative APR may have the potential to predict a robust APR and subsequent complications such as infection [32,33], systemic inflationary response syndrome state [34], and mortality [35]. This relationship is important in the context of patients undergoing surgery with chronic conditions that persistently upregulate the APR, including coronary artery disease, diabetes, and chronic pulmonary disease [36–38]. Early identification of patients at risk of postoperative complications will allow for preoperative mitigation of modifiable risk factors and alterations to postoperative protocols, such as augmented thromboprophylaxis and therapies aimed at resolving the APR. Taken as a whole, these results provide the foundation for future studies investigating the impact of elevated preoperative inflammatory markers due to trauma, infection, or chronic inflammatory conditions on postoperative outcomes.

Acknowledgments

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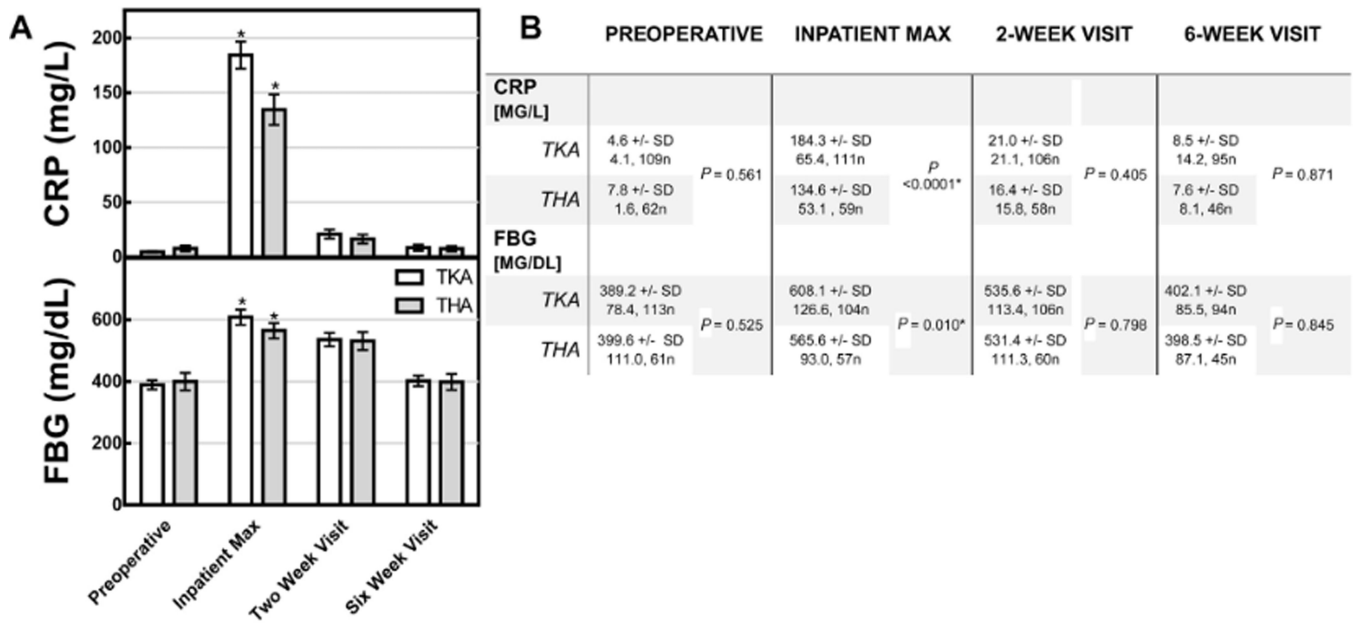38. Koenig W, Rosenson RS. Acute-phase reactants and coronary heart disease. Semin Vasc Med 2002;02:417.

B	PREOPERATIVE		INPATIENT MAX		2-WEEK VISIT		6-WEEK VISIT	
CRP [MG/L]								
TKA	4.6 +/- SD 4.1, 109n		184.3 +/- SD 65.4, 111n		21.0 +/- SD 21.1, 106n		8.5 +/- SD 14.2, 95n	
		$P = 0.561$		$P < 0.0001*$		$P = 0.405$		$P = 0.871$
THA	7.8 +/- SD 1.6, 62n		134.6 +/- SD 53.1, 59n		16.4 +/- SD 15.8, 58n		7.6 +/- SD 8.1, 46n	
FBG [MG/DL]								
TKA	389.2 +/- SD 78.4, 113n		608.1 +/- SD 126.6, 104n		535.6 +/- SD 113.4, 106n		402.1 +/- SD 85.5, 94n	
		$P = 0.525$		$P = 0.010*$		$P = 0.798$		$P = 0.845$
THA	399.6 +/- SD 111.0, 61n		565.6 +/- SD 93.0, 57n		531.4 +/- SD 111.3, 60n		398.5 +/- SD 87.1, 45n	

Fig. 1.

The perioperative rise and fall of 2 acute phase markers. (A) Mean circulating levels of CRP and FBG in response to TKA and THA in the study populations. Y-error bars depict a CI of 95%, and asterisks indicate significant difference between cohorts. (B) Unpaired *t* tests were performed to compare groups. Statistical significance denoted by * and defined as *P* < .05. CRP, C-reactive protein; FBG, fibrinogen; TKA, total knee arthroplasty; THA, total hip arthroplasty; CI, confidence interval; SD, standard deviation.
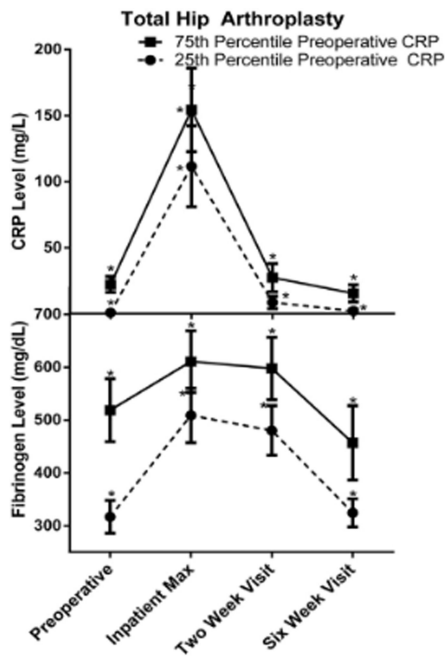
Total Hip Arthroplasty
- 75th Percentile Preoperative CRP
- 25th Percentile Preoperative CRP

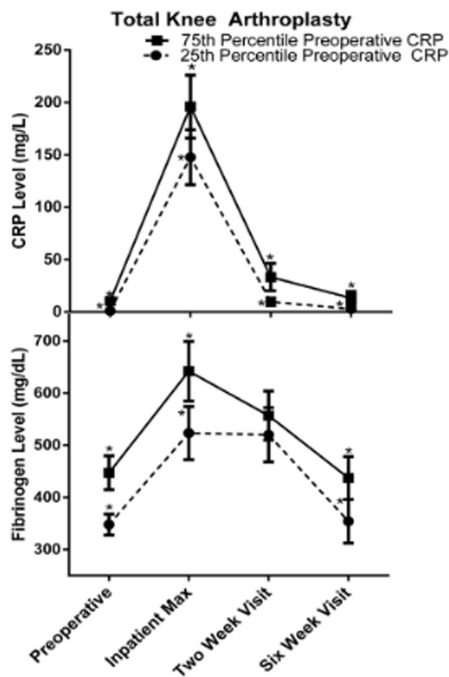| THA	Preoperative CRP Cutoff [mg/L]	Preoperative CRP [mg/L]	Inpatient Max CRP [mg/L]	2-Week Max CRP [mg/L]	6-Week Max CRP [mg/L]
75th	< 11.1	22.2 +/- SD 11.4, 16n	154.3 +/- SD 49.9, 12n	27.3 +/- SN 19.2, 15n	15.4 +/- SD 10.22, 12n
25th	> 1.3	0.8 +/- SD 0.3, 16n	111.6 +/- SD 55.4, 15n	8.5 +/- SD 8.6, 15n	2.1 +/- SD 2.1, 11n
p Value		p<0.0001*	p<0.048*	p<0.0018*	p<0.0001*

THA	Preoperative CRP Cutoff [mg/L]	Preoperative Fibrinogen [mg/dL]	Inpatient Max Fibrinogen [mg/dL]	2-Week Max Fibrinogen [mg/dL]	6-Week Max Fibrinogen [mg/dL]
75th	< 11.1	518.5 +/- SD 107.5, 15n	610.6 +/- SD 92, 12n	597.6 +/- SD 106.5, 15n	456.7 +/- SD 104.6, 11n
25th	> 1.3	316.7 +/- SD 56.2, 15n	508.7 +/- SD 89.4, 14n	480.2 +/- SD 88.3, 16n	324.3 +/- SD 39.5, 11n
p Value		p<0.0001*	p= 0.0087*	p=0.0023*	p=0.00083*

Fig. 2.

The influence of preoperative CRP on the rise and fall of mean fibrinogen following THA. Cohorts defined by the 25th or 75th percentile of preoperative CRP. Y-error bars depict a CI of 95%, and * indicates significant difference between the 25th and 75th percentile. Unpaired *t* tests were performed to compare groups. Statistical significance denoted by * and defined as *P* < .05.

TKA	Preoperative CRP Cutoff [mg/L]	Preoperative CRP [mg/L]	Inpatient Max CRP [mg/L]	2-Week Max CRP [mg/L]	6-Week Max CRP [mg/L]
75th	< 6.4	10.1 +/- SD 4.1, 28n	196.0 +/- SD 74.4, 26n	33.2 +/- SD 31.6, 25n	13.3 +/- SD 14.9, 24n
25th	> 1.8	1.0 +/- SD 0.5, 27n	147.8 +/- SD 59.4, 22n	9.7 +/- SD 8.2, 23n	2.7 +/- SD 4.6, 21n
p Value		p < 0.0001*	p = 0.018*	p = 0.0012*	p = 0.0034*

TKA	Preoperative CRP Cutoff [mg/L]	Preoperative Fibrinogen [mg/dL]	Inpatient Max Fibrinogen [mg/dL]	2-Week Max Fibrinogen [mg/dL]	6-Week Max Fibrinogen [mg/dL]
75th	< 6.4	447.0 +/- SD 81.8, 27n	642.0 +/- SD 132.5, 23n	557.0 +/- 111.2, 24n	437.1 +/- SD 95.4, 23n
25th	> 1.8	347.7 +/- SD 50.4, 27n	523.4 +/- SD 111.7, 21n	520.0 +/- SD 123.7, 24n	354.0 +/- SD 89.2, 20n
p Value		p < 0.0001*	p = 0.0027*	p = 0.28	p = 0.0054*

Fig. 3.

The influence of preoperative CRP on the rise and fall of mean fibrinogen following TKA. Cohorts defined by the 25th or 75th percentile of preoperative CRP. Y-error bars depict a CI of 95%, and * indicates significant difference between the 25th and 75th percentile. Unpaired *t* tests were performed to compare groups. Statistical significance denoted by * and defined as *P* < .05.
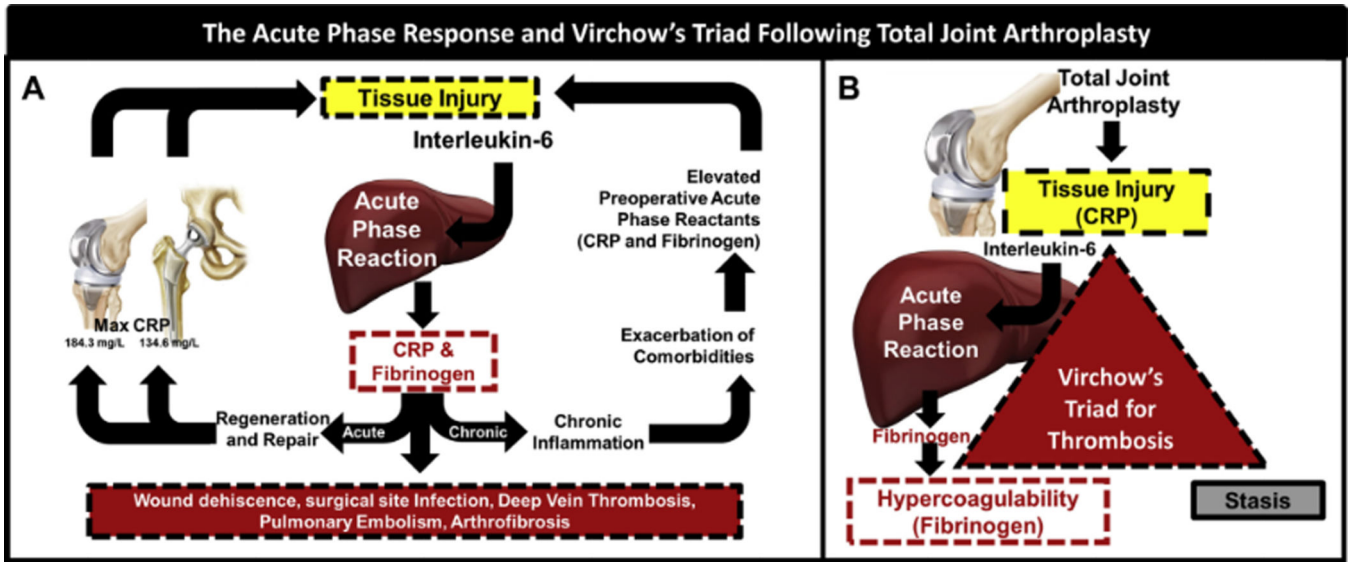
Fig. 4.

The acute phase response (APR) and Virchow's triad following total joint arthroplasty. (A) Damage induced by surgery initiates the acute phase response, a necessary component of wound healing. An unresolved acute phase response can result in chronic inflammation which further elevates acute phase reactants. While the APR is necessary for tissue regeneration, the lack of resolution can lead to life-threatening coagulopathies and poor wound healing. (B) The intersection of the Virchow's triad and the acute phase response. CRP, a short half-life acute phase reactant, peaks close to the time of injury. As such, CRP is highly associated with injury. Fibrinogen, a long half-life acute phase reactant, is an integral factor in hemostasis and can lead to hypercoagulable states if elevated. Thus, CRP and fibrinogen are directly related to 2 components of Virchow's triad: tissue injury and hypercoagulability.

Table 1

Sample Demographics of Patients Undergoing Total Knee Arthroplasty and Total Hip Arthroplasty.

Demographics	Total Knee Arthroplasty	Total Hip Arthroplasty
Number (n)	118	62
Age	64 (55.8–86.0)	58 (46.5–65.0)
Gender	64 Female/54 male	30 Female/34 male
Mean Charlson Comorbidity Index	0 (0–1)	0 (0–1)
Postoperative complications at 6 wk	0	0

Values presented as median and 25th and 75th interquartile range or absolute number. Unpaired, nonparametric Mann-Whitney t tests were used to calculate P values.

Table 2.

Median (25th–75th IQR) Time to Peak Acute Phase Reactant and Resolution Following Total Knee Arthroplasty (TKA) and Total Hip Arthroplasty (THA).

Acute Phase Reactants	Time to Max (d)		Resolution of Max at 2 wk (%)		Resolution of Max at 6 wk (%)	
CRP						
TKA	2.5 (1.7–2.7), 102n	$P<.0001$*	93.4 (87.3–97.5), 87n	$P<.0001$*	99.5% (97.5–100.6), 74n	$P=.247$
THA	1.7 (1.6–1.8), 58n		95.2 (92.5–99.2), 52n		99.5% (97.7–101.6), 41n	
FBG						
TKA	2.8 (2.5–12.2), 91n	$P=.267$	41.0 (0.0–72.5), 83n	$P=.015$*	95.6% (80.1–116.1), 72n	$P=.155$
THA	2.5 (1.7–13.8), 54n		25.8 (0.0–56.6), 53n		86.7% (58.0–110.0), 38n	

Nonparametric Mann-Whitney unpaired *t* tests were used to determine significance.

*
Statistical significance denoted by and defined as $P<.05$. IQR, interquartile range; CRP, C-reactive protein; FBG, fibrinogen; n, number.

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Table 3.

Prior Studies on CRP Following Total Joint Arthroplasty.

Study	Year	Country	Procedure	Number of Patients	Average Maximum CRP (mg/L)	Days to Maximum CRP	Time to Resolution
Aalto et al	1983	Finland	Uncomplicated primary TDA	40	134	2	<3 wk
Shih et al	1986	Republic of China	Uncomplicated primary THA	50	136	2	<3 wk
White et al	1998	United Kingdom	Uncomplicated primary THA	13	100.4	3	>2 wk
			Uncomplicated primary TKA	13	154.9	2	>2 wk
Bilgen et al	2001	Turkey	Uncomplicated primary THA	12	232	2	<3 wk
			Uncomplicated primary TKA	16	260	2	<2 mo
Yombi et al	2015	Belgium	Minimally invasive TKA	807	162	2	<3 wk
			Conventional TKA	249	156	2	<6 wk

CRP, C-reactive protein; THA, total hip arthroplasty; TKA, total knee arthroplasty.