

Correlation between Progress of D-Dimer Following Total Joint Arthroplasty and Early Postoperative Wound and Joint Infection

Total Eklem Artroplastisini Takiben D-Dimer'in Progresyonu ile Erken Postoperatif Yara ve Eklem Enfeksiyonu Arasındaki İlişki

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Öz

Eklem artroplastisi sonrası postoperatif enfeksiyon, azımsanamayacak derecede insidansı olan kötü bir komplikasyondur ve erken tespiti önemlidir. Bu retrospektif çalışmanın amacı, eklem artroplastisi sonrası postoperatif D-Dimer düzeyindeki değişimi diğer proinflatuar mediatörlerle birlikte değerlendirmek ve D-Dimer progresyonu ile erken postoperatif yara enfeksiyonu arasındaki ilişkiyi belirlemektir. Ocak 2017'den Mart 2018'e kadar, elektif primer total kalça artroplastisi (49 hasta) veya total dizartroplastisi (72 hasta) ameliyatı yapılan 121 hastanın retrospektif bir değerlendirmesi yapıldı. CRP, INR, troponin ve D-Dimer düzeyleri preoperatif 1. gün, postoperatif 1., 3., 7., 14. Günlerde kaydedildi ve perioperatif değişiklikler karşılaştırıldı. Tüm hastalar enfeksiyon açısından takip edildi. Çalışmaya toplam 121 hasta (% 76.9 kadın, % 23.1 erkek) dahil edildi. Postoperatif CRP ve INR değerlerinin değişkenliği benzerdi. D-Dimer erken postoperatif dönemde CRP'den daha hızlı yükselme ve düşüş gösterdi. Postoperatif dönemde artan akut faz reaktanları olan CRP ve D-Dimer'in eş zamanlı yükselmesinin ardından, enfeksiyondan bağımsız olarak süreç içinde CRP'nin normal değerlerine dönerken D-Dimer'in tekrar pik yaptığı görüldü. Yirmi dört hastada (%19.8) erken yara enfeksiyonu tespit edildi ve yara enfeksiyonu olan hastaların %70'inde erken postoperatif D-Dimer artışı görüldü ve ayrıca erken dönemde yara enfeksiyonu olan hastalardaki CRP düzeyindeki artış ile D-Dimer yükselişi arasında anlamlı bir ilişki bulundu ($p<0.05$). Postoperatif takip döneminde D-Dimer değerlerinin dalgalanması ve dengesizliği, güçlü bir enfeksiyon göstergesi olarak kullanılmasının olası olmadığını düşündürmektedir. Sadece D-Dimer seviyeleri diğer enflatuar araçlarla kombine edilerek değerlendirilirse, eklem artroplastisi sonrası enfeksiyonunun erken tespitinde etkili olabilir.

Anahtar Kelimeler: Artroplasti, CRP, D-Dimer, Periprotetik Yara enfeksiyonu

Abstract

Postoperative infection after joint arthroplasty is a bad complication with incontrovertible incidence and early detection is essential. The purpose of this retrospective study was to evaluate postoperative change of D-Dimer level after joint arthroplasty along with other proinflammatory mediators and to determine the correlation between progress of D-Dimer and early postoperative infection. From January 2017 until March 2018, a retrospective evaluation of 121 patients operated for elective primary total hip arthroplasty (49 patients) or total knee arthroplasty (72 patients) was conducted. CRP, INR, troponin and D-Dimer level were noted on the preoperative day 1, postoperative days 1, 3, 7, 14 and perioperative changes compared. All patients were followed up for infection. 121 patients included in the study. The variability of postoperative CRP and INR values was similar. D-Dimer showed a more rapid rise and fall than CRP in early postoperative period. Early wound infections were detected in 24 patients (19.8%) and 70% of the patients with wound infection had early postoperative D-Dimer increase and also a significant relationship was found between the patients with wound infection in the early period and the increase in CRP level ($p<0.05$). The fluctuation and instability of D-Dimer values during the postoperative follow-up period suggests that it may be unlikely to be used as a strong indicator of infection. If only the D-Dimer levels combined with other inflammatory mediators like CRP etc. then it might be effective in early detection of wound infection after joint arthroplasty.

Keywords: Arthroplasty, CRP, D-Dimer, Periprotetic Wound Infection

Introduction

Postoperative wound infection after joint arthroplasty is an undesirable result for individual

patients as well as the global health care industry with incontrovertible incidence. Early detection, convenient attention and management protocols are critical to restore and secure the adequate joint functions and morbidity.

C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and white blood cell (WBC) count are conventionally used to spot these infections. D-Dimer level also change rapidly during the postoperative period and have a brief half-life. Analysis of plasma D-Dimer has been revealed as an advantageous diagnostic test in suspected deep vein thrombosis (DVT) before definitive radiological research (1,2). However, the role of D-Dimer in the diagnosis of DVT in patients undergoing total hip replacement and total knee replacement is controversial (3,4).

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D-Dimer is the smallest fragment of fibrin hydrolysis via the fibrinolytic enzyme after cross-linking of the fibrin monomers by activating factor XIII. D-Dimer is a specific molecular indicator of thrombin activation and fibrinolysis and could be used as an acute phase reactant (5). D-Dimer in plasma is often used for deep vein thrombosis exclusion in clinics due to its high sensitivity and easy detection (6).

The acute phase reactants such as CRP can affect multiple stages of inflammation and CRP has been shown to have both proinflammatory and anti-inflammatory actions. Proinflammatory effects of CRP include complement system activation and the initiation of the inflammatory cytokines and shedding of the IL-6 receptor (9-11). Therefore, CRP counters to tissue injury and it may exacerbate tissue damage in some manners (12). Elevation of CRP arises by all means of acute and chronic inflammation due to various causes, including infections and inflammatory disorders.

International normalized ratio (INR) is the conventional test for patients taking vitamin K antagonists. It can also be used to estimate hemorrhage or coagulation status of the patient (13). In literature, it is also reported that infection presented a higher INR level compared to patients without infection (14).

Troponins are formed by three regulatory proteins (troponin C, troponin I, and troponin T) that function in skeletal and cardiac muscle contraction, but not in smooth muscle. Serum troponin level is widely used as a diagnostic marker for stroke, although its low sensitivity. Troponin I and T which are known as cardiac specific markers are largely used in the management and prognosis of cardiac pathologies (15). Troponin may show impermanent elevation in some situations, and may be related to increased membrane permeability such as infection (16).

The purpose of this retrospective study was to evaluate postoperative change of serum D-Dimer level related to wound arthroplasty, which can result in joint infection, along with INR, CRP and troponin.

Material and Method

A retrospective study was conducted in our institute between January 2017 until March 2018. The study was approved by a local University Ethics Committee for Clinical Trials. 49 patients who underwent total hip arthroplasty, 72 patients that underwent total knee arthroplasty were included in the study. A total of 121 patients (76.9% female, and 23.1% male) evaluated. The average age was found as 74 ± 10.42 and ranged between 59 to 94.

Patients who received elective primary total hip arthroplasty or total knee arthroplasty due to osteoarthritis between January 2017 until March 2018 in our institute were included in the study.

Patients with inflammatory arthritis, DVT, revision arthroplasty and who have missing data at all specified times are excluded from the study.

All total knee arthroplasties were performed under tourniquet with a midline skin incision and a medial parapatellar approach. All arthroplasties were performed with cement and hemovac drainage was used for 48 hours postoperatively. All total hip arthroplasties were performed with the posterior approach. The femoral stem and acetabular cup were inserted without cement. Hemovac drainage after THA was also used for 48 hours postoperatively.

Postoperatively, all patients received intravenous antibiotic prophylaxis (3x1 gr/day cefuroxime) routinely until postoperative day 3, unless there was another indication. As medical prophylaxis of DVT, enoxaparin sodium (1x0.4 cc/day) was administered until week 4 postoperatively. Antithrombotic compression stockings were also applied for mechanical prophylaxis. Heterotrophic ossification prophylaxis was not routinely performed. Hemovac drainage was removed postoperative day 2. After drainage removal, patients were mobilized with weight-bearing exercises.

CRP, D-Dimer, INR and troponin levels were collected preoperative day 1, postoperative days 1, 3, 7, and 14 and the changes were compared. All patients were followed up for wound infection.

The distributions of the measured variables of D-Dimer, troponin, INR, CRP were investigated using Shapiro – Wilk test of normality. Measured variables were detailed with median and interquartile range, and tested with Friedman test. Taking steps further with time-wise repeated measures, Post-hoc tests were performed using Wilcoxon and p values were adjusted with Bonferroni correction. Post hoc analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied, resulting in a significance level set at $p < 0.05$. Additionally, Boxplots were created for each measured variable. Correlation coefficient was calculated to understand the relationship between measured variables. Statistical analyses were conducted using SPSS version 25 (made by SPSS Incorporated, located in Chicago, Illinois, USA). The significance level was set at $p < 0.05$.

Results

A total of 121 patients (76.9% female, and 23.1% male) included in the study. The average age was found as 74 ± 10.42 and ranged between 59 to 94. Mean and standard deviation (SD) values for D-Dimer, troponin, INR, and CRP were presented in Table 1.

Repeated measures analysis results revealed that D-Dimer differed significantly between the time points in overall ($p < 0.001$). D-Dimer sharply elevated from preoperative values and peaked at the postoperative day 1 and decreased rapidly at

postoperative day 3 and increased and decreased at postoperative day 7 and 14 respectively. According to the pairwise comparison (Table 2), change between preoperative D-Dimer level to postoperative day 1, day 1 to day 3, day 3 to day 7 was found statistically significant at $p < 0.001$. The similarity of the elevation pattern of D-Dimer in conjunction with CRP was not statistically significant. INR and CRP parameters both showed similar elevations and decreases except the change between postoperative day 4 to day 5 (Figure 1). Additionally, the changes reported for INR and CRP were also significant in overall ($p < 0.001$). Troponin variation over the time was not statistically significant ($p = 0.173$).

According to the correlation test results (Table 3); there was a moderate ($r = 0.462$), positive, and significant correlation between age and D-Dimer and also there was a moderate to strong, positive, and significant correlation between age and preoperative CRP, INR and troponin values.

Early wound infections were detected in 24 patients (19.8%). 17 patients with wound infection (70.8%) had early postoperative D-Dimer increase. When the CRP values were examined, early postoperative CRP increase was detected in all patients (24 patients) with early wound infection. When CRP and D-Dimer results were examined, it was observed that early wound infections were correlated with CRP and D-Dimer levels.

Discussion

D-Dimer is an antigen resulting from fibrin degradation. Elevation of plasma D-Dimer level is a decisive indicator of thrombus formation. D-Dimer is a distinctive marker of fibrinolysis and fibrin formation, making it an important and useful marker for ruling out venous thromboembolism. There are several clinical conditions leading to an increased D-Dimer like venous thromboembolism, infection, tumor, disseminated intravascular coagulation (DIC), recent surgeries, ischemic cardiomyopathy, trauma, stroke, peripheral arteriopathy, aneurysm, congestive heart failure, hemolysis, pregnancy, acute respiratory distress syndrome, liver and kidney failure and inflammatory bowel disease. When the clinical malfunctions that cause the D-Dimer elevation are ruled out, this entity should be useful in determining any human infection. Various studies have exposed that local and systemic infections result in fibrinolytic activities, which cause D-Dimer elevation (17,18). Rodelo et al. reported that elevated D-Dimer level were related with a 28-day mortality in sepsis and they underlined the prognostic value of D-Dimer in sepsis (19).

In a study by Lee et al. perioperative changes of serum markers were compared in primary total knee or hip arthroplasty. They analyzed 65 arthroplasty applied patients to assess postoperative D-Dimer

level after joint arthroplasty along with sedimentation (ESR) and CRP level. ESR increased from postoperative day 1 (max. 45 mm/h) and high level persisted for 6 weeks. CRP elevated from day one as well and stayed high for about 2 weeks. Finally, they reported that D-Dimer level was rapidly elevated at postoperative day 1 and started to decrease to its base level at postoperative day 2 it made a second peak at postoperative week 2. In this study, it is specified that the rise of D-Dimer in the postoperative period may provide useful information such as ESR and CRP which are used as markers of infection. The D-Dimer level might be an effective marker in early exposure of periprosthetic wound and joint infection (PJI) (20).

Shahi et al. fulfilled a study to investigate the D-Dimer pattern in periprosthetic wound and joint infections. They examined CRP, D-Dimer and ESR values in 245 patients to find out the availability of serum D-Dimer level as an indicator of periprosthetic wound and joint infections. In consonance with Musculoskeletal Infection Society Criteria, they determined that serum D-Dimer level showed a higher standing in periprosthetic infections. It was noteworthy that the serum D-Dimer level was more specific and sensitive than ESR and CRP. In this study Shahi et. al measured the specificity of D-Dimer as 93% and the sensitivity as 89% while ESR and CRP showed a sensitivity of 73% and 79% and a specificity of 78% and 80%, respectively. The merged sensitivity and specificity of ESR and CRP were 84% and 47%, respectively. As a result, the authors stated that serum D-Dimer measurement was more useful in determining the infections of the joint prosthesis than serum ESR and CRP level. They also specified that serum D-Dimer level can be used as a determinant for the time of re-arthroplasty in cases requiring revision (21).

Hu et al. organized a retrospective study showing 40 patients with periprosthetic wound and joint infection, 37 patients with aseptic loosening and 59 patients with extra-articular infections in a total number of 136 patients. They collected the serum level of D-Dimer, CRP and ESR and analyzed the results, which were compatible with periprosthetic joint infections. The mean D-Dimer level was significantly higher in patients with PJI. According to the authors, the serum D-Dimer test revealed better sensitivity (87.5%), and better specificity (89.19%); while the serum CRP and ESR had a sensitivity of 80% and 82.5% and a specificity of 78.38% and 64.86%, respectively to diagnose PJI. In conclusion, it was emitted that PJI patients had higher D-Dimer level, which might be a promising indicator to diagnose of PJI (22).

When the literature is explored, although there are some studies indicating that the use of D-Dimer as an infection marker is reliable, there are also skeptical studies that D-Dimer alone may be a weak indicator in this regard as in our study. According to

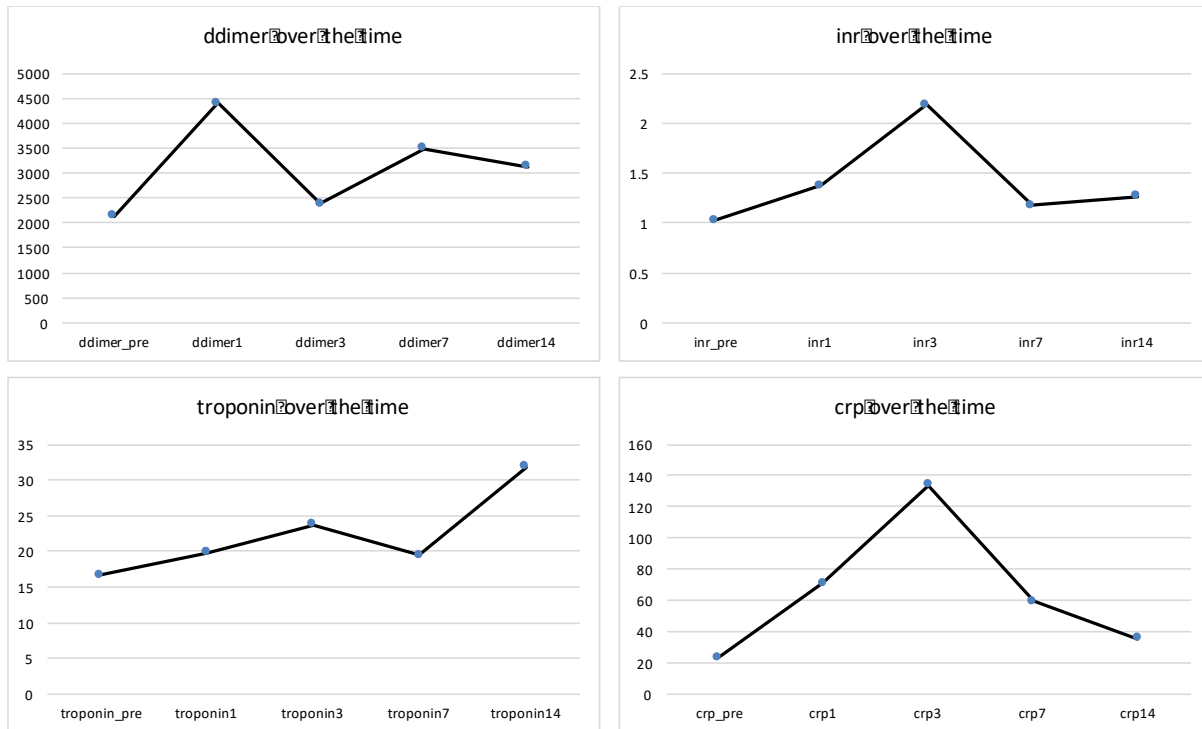


Figure 1. Measured parameter dispersion over the time

Table 1. D-dimer over time

Variable	Mean	SD	Minimum	Maximum	Q1	Q2	Q3	IQR	Mean Rank	p
ddimer_pre	2997.80	3384.38	114.00	10599.00	319.00	928.00	5634.75	5315.75	2.37	0.000
ddimer1	4741.37	2583.19	578.00	9679.00	2596.75	4161.00	6650.25	4053.50	3.95	
ddimer3	2459.07	1680.79	503.00	8602.00	1329.50	1825.00	3241.50	1912.00	2.32	
ddimer7	3725.10	1716.03	906.00	8023.00	2315.75	3656.00	4559.25	2243.50	3.55	
ddimer14	3023.83	1912.81	103.00	10349.00	1890.25	2600.50	3880.50	1990.25	2.82	

p is obtained with Friedman test

Table 2. Pairwise comparison

Time	To compare	ddimer		troponin		inr		crp	
		md	p	md	p	md	p	md	p
pre	1	-1743.6	0.001	-1.9	0.474	-0.7	0.287	-47.1	<0.001
	3	538.7	0.221	-8.4	0.150	-2.4	0.316	-130.9	<0.001
	7	-727.3	0.114	-3.9	0.176	-0.3	0.258	-43.9	<0.001
	14	-26	0.952	-11.8	0.076	-0.2	0.378	-12	0.243
1	pre	1743.6	0.001	1.9	0.474	0.7	0.287	47.1	<0.001
	3	2282.3	<0.001	-6.5	0.269	-1.7	0.327	-83.7	<0.001
	7	1016.3	0.002	-2	0.544	0.4	0.311	3.2	0.784
	14	1717.5	<0.001	-9.9	0.193	0.4	0.235	35.1	<0.001
3	pre	-538.7	0.221	8.4	0.150	2.4	0.316	130.9	<0.001
	3	-2282.3	<0.001	6.5	0.269	1.7	0.327	83.7	<0.001
	7	-1266	<0.001	4.5	0.274	2.1	0.324	86.9	<0.001
	14	-564.8	0.037	-3.4	0.690	2.2	0.309	118.8	<0.001
7	pre	727.3	0.114	3.9	0.176	0.3	0.258	43.9	<0.001
	1	-1016.3	0.002	2	0.544	-0.4	0.311	-3.2	0.784
	3	1266	<0.001	-4.5	0.274	-2.1	0.324	-86.9	<0.001
	14	701.3	0.004	-7.9	0.231	0.1	0.086	31.9	<0.001
14	pre	26	0.952	11.8	0.076	0.2	0.378	12	0.243
	1	-1717.5	<0.001	9.9	0.193	-0.4	0.235	-35.1	<0.001
	3	564.8	0.037	3.4	0.690	-2.2	0.309	-118.8	<0.001
	7	-701.3	0.004	7.9	0.231	-0.1	0.086	-31.9	<0.001

md: mean difference

Table 3. Spearman correlation coefficients

	age	dimer_pre	dimer1	dimer3	dimer7	dimer14	troponin_pre	troponin1	troponin3	troponin7	troponin14	inr_pre	inr1	inr3	inr7	inr14	crp_pre	crp1	crp3	crp7	
dimer_pre	0.482**																				
dimer1	0.287	0.145																			
dimer3	0.168	0.342**	0.15																		
dimer7	0.134	0.308**	0.292**	0.428**																	
dimer14	0.095	0.118	0.236	0.349**	0.563**																
troponin_pre	0.455**	0.306**	0.190*	0.121	-0.028	0.046															
troponin1	0.555**	0.250**	0.209*	0.116	-0.019	-0.094	0.690**														
troponin3	0.577**	0.406**	0.312**	0.251**	0.112	0.029	0.669**	0.688**													
troponin7	0.505**	0.298**	0.198*	0.235*	-0.009	0.014	0.654**	0.665**	0.817**												
troponin14	0.579**	0.406**	0.311*	0.195	0.017	0.023	0.779**	0.677**	0.773**	0.857**											
inr_pre	0.562**	0.458**	0.384**	0.278**	-0.067	-0.176	0.386**	0.349**	0.355**	0.339**	0.549**										
inr1	0.322	0.281**	0.154	0.118	-0.077	-0.249	0.208*	0.155	0.309**	0.226*	0.385**	0.622**									
inr3	0.478**	0.255*	0.165*	0.043	-0.042	-0.155	0.225*	0.151	0.222*	0.149	0.288*	0.555**	0.609**								
inr7	0.311	0.239**	0.278**	0.092	-0.209*	-0.135	0.332**	0.192*	0.246**	0.317**	0.417**	0.522**	0.565**	0.552**							
inr14	0.319	0.280*	0.143	-0.034	-0.075	-0.159	0.351**	0.201	0.336**	0.300*	0.316*	0.573**	0.615**	0.524**	0.574**						
crp_pre	0.779**	0.287**	0.021	0.07	0.207**	-0.121	0.267**	0.281**	0.275**	0.257**	0.453**	0.407**	0.247**	0.341**	0.260**	0.257					
crp1	0.472*	0.348**	-0.301	0.145	0.081	-0.062	0.341**	0.219*	0.169*	0.200**	0.505**	0.270**	0.157	0.113	0.288*	0.552**					
crp3	0.166	0.169	0.088	0.151	0.152	0.175	-0.015	0.012	0.083	0.09	0.134	0.059	0.075	0.146	0.1	0.049	0.308**	0.424**			
crp7	0.333	0.175	-0.001	0.044	-0.042	-0.044	0.103	0.165	0.147	0.215*	0.201	0.083	0.036	0.16	0.26	0.270**	0.387**	0.442**	0.424**		
crp14	0.555**	0.308*	0.115	-0.054	0.016	-0.155	0.415**	0.475**	0.386**	0.408**	0.485**	0.365**	0.223	0.222	0.172	0.473**	0.401**	0.442**	0.348**	0.607**	

*p<0.05, **p<0.01

Pannu, serum D-Dimer has low accuracy to discriminate between septic and aseptic joints that require prosthetic replacements. A retrospective analysis was achieved on a series of 172 revision total knee and/or hip arthroplasties of which 111 were eligible in the final analysis by Pannu et al. As a result, it was specified that there was no statistically significant distinction between septic and aseptic loosening. Although D-Dimer had shown high sensitivity (95.9%), it also displayed a low specificity (32.3%) (23).

Considering the absence of a precise test, the Musculo-skeletal Infection Association (MSIS) presented a series of diagnostic criteria that have recently been amended by the International Consensus Meeting (ICM) on Periprosthetic Joint Infections (PJI). This guide is based on major and minor criteria which involve elevated serum CRP and ESR as well. MSIS criteria modified by the ICM are currently widely accepted in joint prosthetic infections. The research on markers such as D-Dimer in the diagnosis of infection is promising. The base limit for serum D-Dimer in relation to wound and joint was determined as 850 ng/mL. Because of the higher specificity and sensitivity, serum D-Dimer has been shown to perform better than other traditional tests such as ESR and CRP, which are still an important part of ICM criteria, and are included in the new recommended diagnostic criteria for PJI that accurately diagnose infection. As a result of the meeting, high D-Dimer level was presented as indicative of wound and joint infection diagnosis in joint arthroplasty (24).

The other issue concerns the lack of a decisive and easy-to-perform test that may help determining the optimal timing of implant re-implementation. ESR and CRP level are not accepted as a reliable marker in this manner, as they usually increase in the postoperative period (25,26). For that reason, we included some other mediators like INR and troponin to our study, which may also indicate a postoperative infectious process.

D-Dimer is an inexpensive and easy-to-apply test that is becoming increasingly popular in diagnosis and treatment evaluation. The value of D-Dimer measurement in inflammatory conditions such as infection has been reported. Our study aimed to analyze whether D-Dimer echoed the inflammatory and infective conditions in patients who went through total joint arthroplasty. Although D-Dimer level presented an elevating pattern, it was noticed

that D-Dimer had a two peak point and the elevation pattern was quite different from other proinflammatory mediators. Therefore, in our study, D-Dimer alone may be misleading in order to indicate an early postoperative wound or joint infection.

In our study, we observed that D-Dimer, CRP, INR and troponin values had positive and significant correlation according to age. In a study conducted by Zhang et al shows that high levels of CRP, PLT, D-Dimer, ASA, and ≥ 65 years of age increase the risk of preoperative deep vein thrombosis in adult patients (27). Also some studies have shown that levels of CRP and D-Dimer increase with healthy or successful ageing as well as in ageing-related disease(s) (28). We think that this positive correlation to age was not due to a disease because in our clinic the patients are always carefully checked before elective surgical treatments like total knee arthroplasty or total hip arthroplasty.

Early wound infections were detected in 24 patients (19.8%). 17 patients with wound infection (70.8%) had early postoperative D-Dimer increase. When the CRP values were examined, early postoperative CRP increase was detected in all patients (24 patients) with early wound infection. When CRP and D-Dimer results were examined, it was observed that early wound infections were correlated with CRP and D-Dimer levels. On the other hand, D-Dimer level which showed a different elevation pattern from other increasing acute phase reactants like CRP and ESR in infective conditions. Only D-Dimer level has a poor leading for detecting infection and we think that D-Dimer is a poor guide about wound infections but if it is correlated with other acute phase reactants, it might be an effective marker to detect early postoperative wound and joint infections.

In conclusion, D-Dimer, CRP, INR and troponin level increase in the postoperative period. Following the simultaneous increase of CRP and D-Dimer, which are both acute phase reactants that increase in the postoperative period, it was observed that D-Dimer peaked again while CRP returned to its normal values within the process independent of infection. Therefore, studying only the change of D-Dimer values seems unlikely to provide information about the development of the infectious process in the patient. When the literature is explored, while it has been stated in some studies that D-Dimer can be used as an indicator of wound and joint infection; we

believe that the fluctuation and instability of D-Dimer values during the postoperative follow-up period also suggests that it may be unlikely to be used as a strong indicator of wound and joint infection. If only the D-Dimer levels combined with other inflammatory mediators like CRP etc. then it might be effective in early detection of infection after joint arthroplasty.

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