

## D-Dimer Levels Mostly Elevated on the Postoperative First Week

### Postoperatif Dönemde D-Dimer Seviyeleri

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**ABSTRACT Objective:** D-dimer has become one of the frequently used parameters in the diagnosis of pulmonary thromboembolism as it is a rapidly resulted test. D-dimer, as it is a fibrin degradation product, can also elevate in trauma, postoperative period, some acute and chronic diseases beside pulmonary thromboembolism. In literature, there is not enough study about D-dimer elevation in postoperative period. The purpose of our study is to determine postoperative D-dimer increase and show in which days this increase occurs. **Material and Methods:** Electively operated 59 patients were included into this study. All patients over 40 years old were administered prophylaxis by low molecular weight heparin in preoperative and postoperative first days. We evaluated D-dimer levels of patients by using latex agglutination test on the first day of preoperative and postoperative 1st, 3rd, 7th and 15th days. **Results:** The dispersal of operated patients: Multinodular goiter (13), cholelithiasis (12), inguinal hernia (10), pilonidal sinus (6), incisional hernia (5), others (13). D-dimer levels were 0,186±0,344 mg/L preoperatively, 0,312±0,346 mg/L on postoperative 1st days, 0,307±0,410 mg/L 3rd day, 0,289±0,443 mg/L 7th day and 0,271±0,527 mg/L 15th day. D-dimer levels were found significantly higher on the 1st and 3rd days when compared to preoperative levels (p<0.001, p<0.001, respectively). **Conclusion:** As a result in the postoperative period D-dimer test is inadequate for the diagnosis of pulmonary embolism.

**Key Words:** Venous thromboembolism; postoperative period; fibrin fragment D

**ÖZET Amaç:** D-dimer pulmoner tromboemboli tanısında en sık kullanılan ve oldukça hızlı sonuçlanan bir testtir. Fibrin yıkım ürünü olan D-dimer pulmoner tromboemboli dışında travma, postoperatif dönem, akut ve kronik bazı hastalıklarda da yükselmektedir. Literatürde postoperatif dönemde D-dimer yüksekliğiyle ilgili yeterli çalışma bulunmamaktadır. Bu çalışmanın amacı postoperatif D-dimer yüksekliğini ve hangi günlerde bu yüksekliğin ortaya çıktığını tespit etmektir. **Ge-reç ve Yöntemler:** Çalışmaya elektif şartlarda opere edilen 59 hasta alındı. Hastaların hepsi 40 yaşın üzerindeki ve preoperatif ve postoperatif 1. günde düşük molekül ağırlıklı heparin profilaksisi uygulandı. Hastaların D-dimer düzeyleri preoperatif ve postoperatif 1, 3, 7 ve 15 günlerde latex aglutinasyon testi ile değerlendirildi. **Bulgular:** Opere hastaların dağılımı: Multinodüler guatr (13), kolelitiazis (12), inguinal herni (10), pilonoidal sinüs (6), insizyonel herni (5), diğerleri (13). D-dimer düzeyleri preoperatif 0,186±0,344 mg/L, postoperatif 1. günde 0,312 ± 0,346 mg/L, postoperatif 3. günde 0,307 ± 0,410 mg/L, postoperatif 7. günde 0,289 ± 0,443 mg/L and postoperatif 15. günde 0,271 ± 0,527 mg/L'di. Postoperatif D-dimer düzeyleri preoperatif düzeyle karşılaştırıldığında 1. ve 3. günlerde istatistiksel olarak anlamlı yüksek bulundu (p< 0.001, p< 0.001, sırasıyla). **Sonuç:** Sonuç olarak postoperatif dönemde D-dimer yüksekliği tek başına pulmoner tromboemboli tanısını koymada yetersizdir.

**Anahtar Kelimeler:** Venöz tromboemboli; postoperatif dönem; D-dimer

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D-dimer, also called as fibrin degradation products is a serological indicator gained importance in recent years in the diagnosis of venous thromboembolism. The level of D-dimer increases in serum after coagulation event.<sup>1</sup> In many studies when evaluated together with venous

doppler ultrasonography, helical computed tomography and D-dimer is found as a test used safely in the exclusion of thromboembolic events.<sup>2,3</sup>

D-dimer can also increase to high levels in trauma, postoperative period, in acute or chronic diseases beside pulmonary embolism (PE). It has a low positive predictive value for diagnosis of a thromboembolic disease, but a very high negative predictive value, with or without other adjunctive studies, approaching 100%.<sup>1</sup> Therefore, D-dimer is assumed as a useful test used for the exclusion of PE diagnosis.<sup>4,5</sup> There is not efficient study showing high level of D-dimer in postoperative period. So, this study was planned for the purpose of determining postoperative D-dimer elevation and showing in which days this elevation occurs.

## MATERIAL AND METHODS

This study was performed with the partnership of Pulmonary Diseases and General Surgery Department of Ankara Ataturk Educational and Research Hospital. The protocol for the study was approved by the Ethics Committee of the hospital and written informed consent was obtained from all patients. D-dimer tests of the cases were studied in the hematology laboratory of the same hospital.

### PATIENTS

Electively operated 59 patients were included into the study. All patients over 40 years old were administered prophylaxis by low molecular weight heparin in preoperative and postoperative first days. All the cases were operated under general anesthesia. Exclusion criteria were smoking, being pregnant, having deep venous thrombosis and accompanying serious systemic disease (eg. congestive heart failure, severe renal or liver disease, diabetes mellitus) and being under age 18. D-dimer levels of the patients were evaluated on the preoperative day and the 1st, 3<sup>rd</sup>, 7<sup>th</sup> and 15<sup>th</sup> days of postoperative periods.

In this study, the cut-off value for the test was determined as 0.15 mg/L, this value determined according to manufacturer instructions. In the cases having D-dimer level above 0.15 mg/L was planned to perform Doppler ultrasonography of lower

extremity and if necessary helical computed (HCT) angiography the evaluation of PE and deep venous thrombosis.

### LABORATORY TESTS

D-dimer measurements performed on freshly collected plasma from a sodium citrated whole blood sample (nine parts of venous blood drawn into one part 3.2 % trisodium citrate). Samples were centrifuged at 1500 g for 15 minutes at 4-10° C and D-dimer level of the plasma was measured. D-dimer level was studied with the latex agglutination test method which was made by using specific monoclonal antibody for D-dimer and developed by AGEN Biomedical (Auto Dimer test Latex AGEN Biomedical Ltd, Australia). The test applied is a quantitative test and values below 0.15 mg/L are evaluated as negative, the values above this value are evaluated as positive. Both blood samples and test components were stored at room temperature before starting the test. Auto Dimer was calibrated by test standard.

### Statistical analyses

Data are presented as means and standard deviation (SD). Statistics between D-dimer levels related to time were examined by Friedman test. In the case of determining difference, Bonferroni correction was made and measurement times were compared by Wilcoxon sign test. Differences between sexuality groups were evaluated by Mann Whitney U test. Relation between operation reasons and D-dimer was evaluated by Kruskal Wallis variance analysis and difference situations were compared by Mann-Whitney U test by making Bonferroni correction. A *p* value of less than 0.05 was considered significant.

## RESULTS

The 59 patients enrolled to this study; with a mean age of  $47.1 \pm 13.9$  years ( $\pm$ SD) [range 18 to 74 years]. 29 (49.2%) of them were male and 30 (50.8%) of them were female. Patients' indications for operation are shown on Table 1 and Figure 1 show the logarithmical spreading graphic of 59 patients according to D-dimer levels.

Groups having more than four patients were chosen for the statistical analysis. These groups

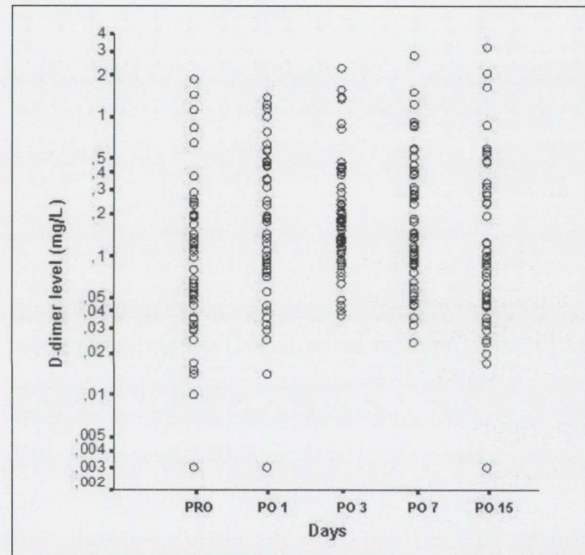
Operation Type	Patients	
	n	%
Multinodular Goiter	13	22
Cholelithiasis	12	20.3
Inguinal hernia	10	16.9
Pilonidal sinus	6	10.2
Incisional hernia	5	8.5
Acute appendicitis	4	6.8
Colon cancer	2	3.4
Breast cancer	1	1.7
Gastric cancer	1	1.7
Medullary thyroid cancer	1	1.7
Diastasis recti	1	1.7
Rectal polyp	1	1.7
Varicose	1	1.7
Hydatic cyst of liver	1	1.7
<b>Total</b>	<b>59</b>	<b>100</b>

were multi-nodular goiter (13 cases), cholelithiasis (12 cases), inguinal hernia (10 cases), pilonidal sinus (6 cases), incisional hernia (5 cases) (Table 2).

Mean D-dimer level of the patients in preoperative period was 0,186 mg/L (min-max: 0,003-1,908). Maximum 1,908 mg/L D-dimer level belonged to the patient being operated for plastron appendicitis. Mean D-dimer level of the patients on the postoperative 1<sup>st</sup> day was 0,312 mg/L (min-max: 0,003-1,382). Maximum level was measured in two different patients. One of them was incisional hernia; the other one was cholelithiasis and both of them had same value (1,382 mg/L). Mean D-dimer value of the patients on the postoperative 3<sup>rd</sup> day was 0,307 mg/L (min-max: 0,032-2,277). A patient

being operated for gastric cancer had the maximum level. Mean D-dimer level of the patients on the postoperative 7<sup>th</sup> day was 0,290 mg/L (min-max: 0,024-2,764). Same patient having the maximum level of D-dimer on the 3<sup>rd</sup> day previously had the maximum level also on the 7<sup>th</sup> day. Mean D-dimer level on the postoperative 15<sup>th</sup> day was 0,272 mg/L (min-max: 0,003-3,170). This maximum level belonged to the same patient being operated for gastric cancer (Table 3).

In comparison with D-dimer levels on postoperative 1<sup>st</sup> and 3<sup>rd</sup> days with preoperative period ( $p < 0.001$  and  $p < 0.001$ , respectively) was significantly high, as shown in Table 4.



**FIGURE 1:** Logarithmic spreading graphic of 59 patients with D-dimer results.

PRO: preoperative, PO 1: postoperative first day, PO 3: postoperative third day, PO 7: postoperative seventh day, PO 15: postoperative fifteenth day.

Operation Indications	Patients n	Preoperative D-dimer(mg/L)		Postoperative D-dimer (ng/mL)							
		Mean±SD	Min-max	1 <sup>st</sup> day		3 <sup>rd</sup> day		7 <sup>th</sup> day		15 <sup>th</sup> day	
				Mean±SD	Min-max	Mean±SD	Min-max	Mean±SD	Min-max	Mean±SD	Min-max
Inguinal hernia	10	0.109±0.126	0.017-0.378	0.228±0.227	0.044-0.637	0.224±0.267	0.038-0.395	0.271±0.441	24-1.506	0.285±0.501	0.036-1.636
Incisional hernia	5	0.240±0.235	0.044-0.642	0.558±0.491	0.185-1.382	0.163±0.033	0.122-0.204	0.333±0.173	0.118-0.520	0.297±0.126	0.126-0.469
Multi-nodular goiter	13	0.255±0.457	0.025-1.422	0.270±0.210	0.036-0.581	0.126±0.105	0.032-0.423	0.123±0.107	0.036-0.382	0.110±0.151	0.017-0.567
Pilonidal sinus	6	0.130±0.109	0.035-0.283	0.160±0.152	0.003-0.360	0.151±0.069	0.048-0.239	0.074±0.048	0.032-0.138	0.121±0.080	0.034-0.237
Cholelithiasis	12	0.154±0.228	0.014-831	0.412±0.501	0.014-1.382	0.479±0.376	0.230-1.561	0.365±0.301	0.048-0.908	0.240±0.269	0.020-0.879
<b>Total</b>	<b>46</b>	<b>0.179±0.285</b>	<b>0.014-1.422</b>	<b>0.315±0.349</b>	<b>0.003-1.382</b>	<b>0.247±0.270</b>	<b>0.032-1.561</b>	<b>0.235±0.283</b>	<b>0.024-1.506</b>	<b>0.204±0.287</b>	<b>0.017-1.636</b>

SD: Standard deviation

**TABLE 3:** D-dimer levels of 59 patients.

Days	mean±SD (mg/L)	min-max (mg/L)
Preoperative day	0.186 ± 0.344	0.003-1.908
Postoperative 1 <sup>st</sup> day	0.312 ± 0.346	0.003-1.382
Postoperative 3 <sup>rd</sup> day	0.307 ± 0.410	0.032-2.277
Postoperative 7 <sup>th</sup> day	0.289 ± 0.443	0.024-2.764
Postoperative 15 <sup>th</sup> day	0.271 ± 0.528	0.003-3.170

**TABLE 4:** P values of D-dimer levels on postoperative days, compared with preoperative values.

Postop. D-dimer (mg/L) mean±SD	Preop. D-dimer(mg/L) mean±SD	p value
1 <sup>st</sup> day 0.312±0.346	0.186±0.344	<0.001*
3 <sup>rd</sup> day 0.307±0.410	0.186±0.344	<0.001*
7 <sup>th</sup> day 0.289±0.443	0.186±0.344	<0.013
15 <sup>th</sup> day 0.271±0.528	0.186±0.344	<0.140

According to Bonferroni correction, only these values were assumed as significant.

There was not any statistically significant difference in females concerning D-dimer level related to time, but there was a significant difference in males on the 1<sup>st</sup> and 3<sup>rd</sup> days when compared to preoperative period ( $p < 0.001$ ,  $p < 0.004$ , respectively).

In the comparison between disease groups; measurements derived from cholelithiasis group were found to be higher than the measurements derived from incisional hernia, multi-nodular goiter, pilonidal sinus groups concerning 3<sup>rd</sup> day measurements ( $p < 0.002$ ,  $p < 0.001$ ,  $p < 0.001$ , respectively).

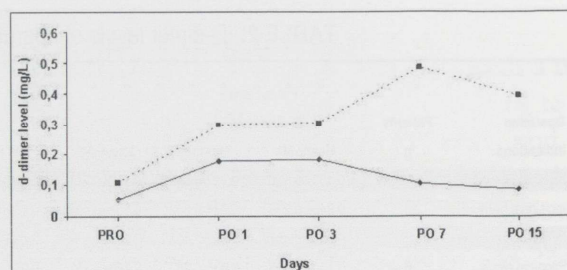
In respect to the measurements of 7<sup>th</sup> day, measurements derived from incisional hernia group were found to be higher than those of multi-nodular goiter group ( $p = 0.07$ ). Similarly, measurements of the group having cholelithiasis were found to be higher than pilonidal sinus group ( $p = 0.007$ ).

In respect to age, between the patients that above 60 years old and below 60 years old, on 7<sup>th</sup> and 15<sup>th</sup> days a significant difference were detected when compared to preoperative period. ( $p < 0.001$ ,  $p = 0.007$ ; respectively) (Figure 2).

Patients having a D-dimer level above 0,15 mg/L were examined for deep venous. Deep venous thrombosis was suspected in seven patients had doppler ultrasonography. Deep venous thromboses were not detected in these patients. No patient had to HCT angiography.

## DISCUSSION

D-dimer level increases when coagulation system is activated. It has been accepted as a useful test for the diagnosis of thromboembolic events for a long time. However; since D-dimer may increase in cases such as any kind of surgical intervention, trauma, tissue damage, infections, pregnancy, disseminated intravascular coagulation, it creates limitations to its diagnostic value.<sup>6-8</sup> There is not sufficient study in literature searching how D-dimer level is affected, when operation variety is taken into consideration. In a study by Codine et al which investigated the contribution of postoperative D-dimer measurement to the diagnosis of venous thromboembolism in patients to whom orthopedic surgery was applied, D-dimer levels were constantly elevated postoperatively (2 to 6 fold above normal). Although D-dimer levels have returned to normal levels in 4 weeks, in some cases remained elevated (3-fold above normal). D-dimer level was not significantly different between patients with deep vein thrombosis and those without.<sup>9</sup> In our study D-dimer levels were found to be significantly high, especially on the 1<sup>st</sup> and 3<sup>rd</sup> days of the postoperative period ( $p < 0.001$ ). It was observed that D-dimer levels of the most patients decreased to its normal limits on the 15<sup>th</sup> day.



**FIGURE 2:** Changes in postoperative D-dimer related to age. PRO: preoperative, PO 1: postoperative first day, PO 3: postoperative third day, PO 7: postoperative seventh day, PO 15: postoperative fifteenth day.

The measurement of preoperative D-dimer levels is considered to be useful for predicting lymph node metastasis and stage of colorectal cancer.<sup>10, 11, 12</sup> There was not such a high level preoperatively in our only patient operated for colon cancer. But, in postoperative period D-dimer levels of the patient elevated on the 3<sup>rd</sup>, the 7<sup>th</sup> and the 15<sup>th</sup> days (1,367 mg/L, 1,229 mg/L, 2,091 mg/L respectively). Embolism was not detected in this patient.

D-dimer increases in the situations where tissue damage is more. In a study made by Chen et al; it was figured out that there was a meaningful correlation between injury severity scale and D-dimer and the activation of the coagulation mechanism increased in severe traumas.<sup>7</sup>

In a study made by Schietroma et al; they investigated hemostatic system alterations in patients who undergo open and laparoscopic cholecystectomy. They observed in patients who had undergone open cholecystectomy activated coagulation more.<sup>6</sup> In the study by Prisco et al on the same subject, they determined an increase in D-dimer levels in both groups after operation, but they didn't find the results statistically meaningful.<sup>13</sup> Martinez-Ramos et al examined the changes in hemostasis in patients applied laparoscopic cholecystectomy; D-dimer levels decreased in the preoperatively determination followed by a significant enhancement immediate postoperatively and 24 hours; it returned to normal basal values on the seventh day. No significant differences were found between the two groups.<sup>14</sup> Rahr et al determined in their study that D-dimer levels increased significantly on the first day after laparoscopic cholecystectomy.<sup>15</sup> Lippi et al studied on D-dimer levels in patients having total elective hip surgery and laparoscopic cholecystectomy. They suggested that the postoperative activation of the hemostatic system depends on the type and time since surgery, thus limiting the clinical usefulness of D-dimer testing in the diagnostic approach to postoperative venous thromboembolism.<sup>16</sup> All the cases in our study were open cholecystectomy and on the 3<sup>rd</sup> day of postoperative period D-dimer values were found statistically higher among the groups of incisional hernia, multinodular goiter and pilonidal sinus ( $p < 0.002$ ,  $p < 0.001$ ,  $p < 0.001$ , respectively).

On the 7<sup>th</sup> day of postoperative period; D-dimer levels of incisional hernia were higher than multi-nodular goiter group, and D-dimer levels of the group having cholelithiasis were higher than pilonidal sinus group ( $p = 0.07$ ,  $p = 0.07$ , respectively). Patients operated for cholelithiasis had no cholecystitis. However; since long time-consuming major operation such as colon cancer and gastric cancer are few in number, there wasn't any opportunity to make a statistical research among them.

Kentaro et al examined whether ambulatory ability before surgery might influence the postoperative D-dimer level after total hip arthroplasty. The results suggest that preoperative low ambulatory ability in patients with osteoarthritis over 60 years might influence the postoperative D-dimer after total hip arthroplasty, indicating the potential risk for postoperative deep venous thrombosis. In the same study, the D-dimer level were different between patients over and under 60 years of age. They suggested that the major reason for this difference could be explained by metabolic change. Furthermore, hormonal changes should be also considered. Post menopause phase may also affect the fibrinolysis system in the veins.<sup>17</sup> In the research by Boldt et al; change in D-dimer level together with the age was determined.<sup>18</sup> We determined a significant increase in D-dimer levels of patient group over 60 years old on the 7<sup>th</sup> and 15<sup>th</sup> days of the postoperative period.

Levy et al performed for the determination of the cutoff value for D-dimer level during the postoperative period. Results suggested that a D-dimer value below 2 micrograms/ml has a negative predictive value of 100%. A D-dimer value over 4 micrograms/ml would indicate suspected deep venous thrombosis in half of the cases, even without clinical signs. They suggested that these two optimum cutoff values are useful for determining the need for further explorations for deep venous thrombosis.<sup>19</sup>

Bounameaux et al showed that in patients who undergoing total knee arthroplasty plasma D-dimer values didn't differ between patients who had DVT and those who had no DVT. In conclusion, plasma measurement of D-dimer level is of no value for predicting, diagnosing or ruling out DVT in pati-

ents undergoing total knee arthroplasty.<sup>20</sup> Peetz et al in 234 trauma surgery patients who administered thrombosis prophylaxis with LMWH was adjusted according to levels of D-dimer. They were divided into a high-risk group and a moderate-risk group. A high-risk group showed significantly higher D-dimer levels than a moderate-risk group. Measurement of D-dimer levels showed a sensitivity of 100% and a specificity 72.8 %.<sup>21</sup>

In this study D-dimer levels were detected more than 0,15 mg/L in 17 cases in the preoperative period. In 3 cases of them, D-dimer levels were detected more than 1,0 mg/L (2 of them were multi-nodular goiter and 1 of them was plastron appendicitis), D-dimer levels decreased in postoperative period. These cases were examined for DVT and pulmonary embolism at the beginning and embolism is not detected.

As a result; increases in postoperative D-dimer may cause error concerning diagnosis in patients

that do not have clinical findings of pulmonary embolism. In the postoperative period, measurement of D-dimer level doesn't aid in diagnosing thromboembolism. In respect to this test may not use to diagnosis of deep venous thrombosis or pulmonary embolism in the early postoperative period. However, in order to be able to give a cut-off value for increments of D-dimer levels for certain disease, new extensive prospective studies must be done in postoperative period. On the other hand, increase of D-dimer in postoperative period might not show the diagnosis of PE. Hence other diagnostic methods (venous doppler ultrasonography, helical BT, lung perfusion sintigraphy) should be use for the diagnosis of this disease. Particularly, it is thought that hypercoagulable state is higher in postoperative first week as defined in literatures.

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