

Investigation of Fibronectin Levels and Immune Response in Patients with Acute Appendicitis

AKUT APANDİSİTLİ HASTALARDA İMMÜN CEVAP VE SERUM FİBRONEKTİN DÜZEYLERİNİN ARAŞTIRILMASI

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Summary

In this study, we investigated serum fibronectin levels and immune response in monitoring infection complications which may develop after operation and in diagnosis of the patients with acute appendicitis. We selected 25 patients with acute appendicitis as well as another 25 who had undergone equivalent degree of surgical trauma as the control group in the study. In both group of patients, we compared the levels of serum fibronectin, immunoglobulin A, G, M (Ig A, Ig G, Ig M), complement 3, 4 (C₃, C₄), C reactive protein (CRP), and leukocyte immediately before the operation, immediately after the operation, at postoperative 1st, 3rd and 7th days. While serum fibronectin levels immediately before and after operation were found to be below the normal levels in the study group, they showed a progressive increase during the postoperative period (p<0.05). When Ig levels were compared with the control group, it was observed that Ig A, Ig G and Ig M levels were normal in the study group before the operation while they showed significant increase at postoperative 3rd and 7th day. However, while there were not any differences in Ig A, Ig G levels in comparisons among the groups, a significant increase was determined in IG M level in the study group (p<0.05).

While there was not any difference in C₃ level in the comparisons with respect to C₃ and C₄ levels, C₄ level in the study group in postoperative 3rd and 7th day showed a significant increase (p<0.01). No change was observed in the control group with respect to leukocyte number, while a progressive decrease was found in the study group during the pre-operation period (p<0.01). Levels of CRP were found to be considerably higher in the study group than the control group before operation (p<0.01). While no change was observed in CRP levels in the control group during the postoperative period, elevated levels in the study group before the operation showed a sharp decrease after the operation (p<0.01).

Serum fibronectin level, when correlated with the other laboratory tests, can be considered as an auxiliary test in diagnosis of intraabdominal infection which can result after operation, and in diagnosing a complicated acute appendicitis before operation.

Key Words: Acute Appendicitis, Fibronectin, Immunological changes

T Klin J Med Res 2002, 20:21-27

T Klin J Med Res 2002, 20

Özet

Bu çalışmada akut apandisit hastalarının tanısında ve ameliyat sonrası gelişebilecek infeksiyöz komplikasyonların izlenmesinde immün cevap ve serum fibronectin düzeyleri araştırıldı. Çalışma grubu olarak eşdeğer cerrahi travma uygulanan 25 hasta çalışmaya alındı. Her iki grupta serum fibronectin seviyeleri, immünglobulin A, G, M (Ig A, Ig G, Ig M) ve kompleman 3, 4 (C₃, C₄) ve C-reaktifprotein (CRP) ile lökosit sayıları hemen ameliyat öncesi, hemen ameliyat sonrası, postoperatif 1., 3., 7. günlerde araştırıldı. Çalışma grubunda serum fibronectin seviyesi hemen ameliyat öncesi ve hemen ameliyat sonrası değerleri normal değerlere göre düşük bulunurken, postoperatif dönemde progressif artış görüldü (p<0.05). Immünglobulin değerleri kontrol grubu ile karşılaştırıldığında IgA, IgG ve IgM seviyeleri çalışma grubunda ameliyat öncesi normal bulunurken postoperatif 3. ve 7. günlerde anlamlı artış gösterdi (p<0.05). Ayrıca grupların karşılaştırılmasında IgA ve IgG seviyeleri açısından herhangi bir fark bulunamazken çalışma grubunda IgM seviyesinde belirgin artış vardı (p<0.05).

C₃ ve C₄ değerlerinin gruplararası karşılaştırılmasında fark bulunmazken, Çalışma grubunda C₄ seviyesinde postoperatif 3. ve 7. günlerde anlamlı artış gözlemlendi (p<0.01). Kontrol grubunda lökosit sayısında anlamlı değişiklik olmazken çalışma grubunda ameliyat öncesine göre progressif azalma oldu (p<0.01). CRP değerlerinde postoperatif dönemde kontrol grubunda değişiklik olmazken çalışma grubunda ameliyat öncesi değere göre belirgin düşme gözlemlendi (p<0.01).

Serum fibronectin ölçümü diğer laboratuvar testleri ile kombine edildiği zaman komplikasyonlu akut apandisitlerin ve ameliyat sonrası gelişebilecek intraabdominal infeksiyonun teşhis edilmesinde kullanılabilir.

Anahtar Kelimeler: Akut apandisit, Fibronectin, İmmün değişiklikler

T Klin Araştırma 2002,20:21-27

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Acute appendicitis, acute inflammation of appendix vermiformis, constitutes approximately 1% of all acute abdominal diseases. Though it is encountered in all age groups, it is more frequent in 20- 30 age group. Recently, it has been shown that appendix is a part of intestinal lymphoid tissue system (1, 2). It is obvious that it will play an important role due to B lymphocyte intensity. B lymphocytes contain 30% IgM, 19% IgA and 12% Ig G(1). Acute appendicitis should be diagnosed timely, and appropriate surgical treatment should be applied. In this case, mortality rate is below 0.1%. Nevertheless, rate of unnecessary appendectomy is still around 20%. This anatomic structure which has an important role in the immune system should not be removed unnecessarily.

Laboratory studies are involved in the diagnosis of acute appendicitis clinic picture along with examination and radiological investigations. In this study, by examining levels of serum fibronectin, immunoglobulin (IG), C-reactive protein (CRP), complement(C) and leukocyte (Leuk), we investigated changes in immune response resulting from acute appendicitis, which is an intraabdominal sepsis. We also examined the role of the changes in these parameters on the clinical diagnosis, course and prognosis of the patient.

Materials and Methods

This study was performed in the 4th General Surgery Clinics of Ankara Training and Research Hospital, on the patients who were operated for acute appendicitis and inguinal hernia during the year 2000 and during the first 3 months of 2001.

A group of 25 patients who had been operated for appendectomy was taken as the study group, and 25 patients with inguinal hernia who had experienced a surgical intervention equal to acute appendicitis trauma were included as the control group. The patients in the two groups were randomly included in the study, without any consideration to age and sex, of which distribution among the groups are given in the Table 1.

Diagnosis of acute appendicitis was established by patient history, clinical and laboratory examinations, and was confirmed histopathologically. Venous blood samples were taken from the both groups just before and after the operation, and at postoperative 1st, 3rd and 7th days; and levels of leukocyte, serum fibronectin, CRP, IgA, Ig G, Ig M, C₃, C₄ were examined. Ig A, G, M, CRP and C₃, C₄ parameters were measured by Nephelometric method (Behring EN II).

Serum fibronectin was determined using Human - Fibronectin (Dade Behring Marburg GmbH) kit, and blood leukocyte number was determined using Beckman / Coulter Gen-S system. Value of 9000/mm³ was considered as high. These tests are completed within 20 minutes in the laboratory.

Statistical Analysis: Each group was evaluated within itself and in comparison with the other group. In statistical evaluation, paired simple t test was employed in-group comparisons, and independent samples test used in comparisons among groups. Value of p<0.05 was accepted as significant.

Table 1. Demographic characteristics of the groups in this study.

| Group | Female | Male | Mean age | Total Subjects |
|---------|--------|------|-------------|----------------|
| Study | 8 | 17 | 24.9(12-60) | 25 |
| Control | 4 | 21 | 50.2(9-66) | 25 |

Results

Levels of serum fibronectin were found to be lower than normal values in the study group, both before and after the operation, while it showed a progressive increase during postoperative period(p<0.05). However, while it was at normal levels in the control group before the operation, a decrease resulting from trauma was observed after the operation, and it showed a progressive increase until postoperative 7th day (p<0.05, Table 2). In the comparison of the both groups, fibronectin levels in the study group was lower immediately before and immediately after operation (p<0.05). Whereas Ig A levels before the operation were normal in both groups, they were found to be significantly higher at 3rd and 7th postoperative days than before operation levels (p<0.05, Table 2). There was not any significant difference in the comparisons among the groups (p>0.05). Levels of Ig G did not show any significant change in the control group,

while they showed a significant increase at 3rd and 7th postoperative days, as compared to the levels before operation (p<0.01, Table 2). No significant difference was observed in the comparisons among the groups (p>0.05). Ig M levels in both groups showed a progressive increase during postoperative period compared with the levels before operation (p<0.01, Table 2). In comparisons among groups, Ig M levels at postoperative 1st, 3rd and 7th days were found to be significantly higher in the study group than in the control group (p<0.01).

C₃ levels in the study group showed a significant increase after postoperative 1st day, compared with the levels before operation (p<0.05, Table 2). But in the control group, it showed a significant decrease right after the postoperative 1st day, and a significant increase at postoperative 3rd and 7th days. No significant difference was observed with regard to the rate of increase in the

Table 2. Levels of fibronectin, immunoglobuline, complement, C reactive protein and leukocyte in the study and control groups.

| Group | Parameter | Before operation X±SD | After operation X±SD | Postop 1 day X±SD | Postop 3 day X±SD | Postop 7 day X±SD | p |
|---------|----------------|--------------------------|-------------------------|----------------------|----------------------|----------------------|-------|
| Study | FN | 13.79 ±5.43 | 16.26 ±6.82 | 19.92 ±10.14 | 22.38 ± 9.42 | 24.82 ±9 | 0.05 |
| | IgA | 1.65 ± 1.06 | 1.67 ±0.97 | 1.74 ±0.95 | 2.04 ± 1.10 | 2.19 ± 1.20 | <0.05 |
| | IgG | 9.87 ±3.07 | 10.15 ±3.42 | 10.36 ± 1.83 | 1.85 ±2.31 | 12.00 ±2.40 | <0.01 |
| | IGM | 1.07 ±0.44 | 1.25 ±0.50 | 1.26 ±0.41 | 1.49 ±0.62 | 1.68 ±0.61 | <0.01 |
| | c ₃ | 1.06 ±0.37 | 1.10 ±0.20 | 1.19 ±0.23 | 1.21 ±0.46 | 1.28 ±0.32 | <0.05 |
| | c ₄ | 0.18 ±0.07 | 0.19 ±0.04 | 0.21 ±0.04 | 0.26 ±0.04 | 0.26 ±0.04 | 0.05 |
| | Leuk | 16700 ±2669 | 13000 ±2960 | 10200 ±2240 | 8600 ±2075 | 8200±1400 | <0.01 |
| | CRP | 123.74 ±54.96 | 95.34 ±40.81 | 63.78 ± 36.27 | 43.92 ±25.08 | 30.75 ±20.99 | 0.01 |
| Control | FN | 29.51 ±6.48 | 20.65 ±3.27 | 21.55 ±4.80 | 23.98 ±4.45 | 25.99 ±4.21 | 0.05 |
| | IgA | 2.06 ±0.40 | 2.11 ±0.48 | 2.10 ±0.44 | 2.21 ±0.48 | 2.28 ±0.45 | <0.05 |
| | IgG | 10.82 ±2.03 | 10.86 ± 1.81 | 10.89 ±2.28 | 10.76 ±2.13 | 11.09 ± 1.88 | >0.05 |
| | IgM | 0.86 ±0.13 | 0.89 ±0.16 | 0.85 ±0.21 | 0.96 ±0.20 | 0.95 ±0.18 | <0.01 |
| | c ₃ | 1.13 ±0.18 | 1.09 ±0.13 | 1.08 ±0.11 | 1.20 ±0.16 | 1.16 ±0.15 | 0.05 |
| | c ₄ | 0.19 ±0.01 | 0.19 ±0.01 | 0.20 ±0.01 | 0.21 ±0.01 | 0.21 ±0.01 | <0.05 |
| | Leuk | 7000±1850 | 7800±1700 | 7600 ±2300 | 7400 ±2100 | 7200±1500 | >0.05 |
| | CRP | 4.2 ±0.81 | 4.4 ±0.83 | 5.8 ±2.11 | 5.3 ± 1.08 | 4.4 ±0.71 | >0.05 |

| Parameter | Normal values | Parameter | Normal values |
|-----------------|---------------|------------------|-----------------|
| Fibronectin(FN) | 25-40 mg/dl | c ₃ | 0.9- 1.8 g/L |
| IgA | 0.7-4 g/L | c ₄ | 0.1 -0.4 g/L |
| IgG | 7-16 g/L | Leukocyte (Leuk) | 7000- 10 000 DL |
| IgM | 0.4 - 2.3 g/L | CRP | 0-3 mg/L |

comparison of the two groups ($p > 0.05$). As for C₄ levels, increases as compared to the levels before operation were observed in starting from the first postoperative day in the study group, and from third postoperative day in the control group ($p < 0.01$, Table 2). In group comparisons, a significant increase was observed at postoperative 3rd and 7th days in the study group ($p < 0.01$). While there was no change in the control group with respect to leukocyte number, a progressive decrease after the operation was observed in the levels before operation in the study group, as the infection source had been removed after the operation ($p < 0.01$). In group comparisons, it was found significantly high in the study group until the postoperative 3 day ($p < 0.01$). CRP levels before operation were much higher in the study group than in the control group ($p < 0.01$). While no change was observed in CRP levels of the control group during the postoperative period, the elevated levels in the study group before the operation showed a sharp decrease after operation ($p < 0.01$). In group comparisons, levels in the study group were found to be higher than in the control group at all times ($p < 0.01$).

Discussion

Diagnosis of acute appendicitis is still a problem among surgical emergency cases. Despite all the technological advances, a diagnosis difficulty rate of about 20% exists(3). The aim of the appendectomy in acute appendicitis is to reduce perforation, thus morbidity and mortality resulting from this. If appropriate treatment is not applied timely, it causes malicious results such as intraabdominal infection and sepsis(4, 5). Acute appendicitis is the most important and frequent causes of intraabdominal sepsis. Factors such as insufficiency of opsonin, perfusion disorders resulting from changes in the hepatic blood flow, or intrinsic macrophage dysfunction may play roles in the development of Reticular Endothelial system(RES) observed during the sepsis.

Fibronectin, which is a high molecular weight protein, is known to be an acute phase reactant

which intervenes with a series of cellular activity. It is also an important opsonine of RES. Studies have shown that serum fibronectin levels have decreased considerably after sepsis, major operations and widespread burns(6-10). Progressive decrease in the fibronectin levels at the beginning or during the clinical course may be considered as a sign of undesired clinical prognosis. For this reason, serum fibronectin may indicate the extent of organ insufficiency, and may help early identification of formation of sepsis. There are studies which have determined high levels of tissue fibronectin in acute appendicitis(11). However, we have encountered no work dealing with serum fibronectin levels in those patients. Taking into consideration the fact that changes might occur in serum fibronectin levels in surgical trauma too, the control group was formed from a group of patients with elective herniography which had an equal trauma intensity to that of appendectomy, without any inflammation or infection presentation. Serum fibronectin levels of the study group was lower than normal levels both right before and right after the operation, while it showed a progressive increase after the operation ($p < 0.05$). Besides, during early postoperative period, decreases were observed in the serum fibronectin levels of the control group, decreases were observed later on. The changes in these levels were not significant either ($p > 0.05$). When the two groups were compared, serum fibronectin levels in the study group were found to be lower right before and right after the operation. Three patients in the appendectomy group developed an injury-location infection after operation, but no correlation was found between this morbidity and serum fibronectin level. Determination of serum fibronectin level by Nephelometric method is both rapid and cost-effective as much as other auxiliary diagnosis methods, and for these reasons, it may be a routinely applied as an examination method. Levels of serum fibronectin may be an early warning sign of septic complications of acute appendicitis or of

localized infections which may develop after appendectomy.

Complement system is known to be activated in sepsis situations. It is accepted here that microorganisms interacts with direct or indirect complement system. Complement activation may appear before clear clinic signs of sepsis have occurred (12). In our study, levels of C_3 started to increase in study group from the postoperative 1st day, whereas increase was seen in the control group from postoperative 3rd day. There was not any significant difference in the comparison of two groups. While elevated C_4 levels were determined in the study and control groups at postoperative 3rd day, the increase rate in the study group was higher postoperative 3rd and 7th day ($p < 0.05$).

In their study on patients with sepsis, Cautinho et al. have shown significant decreases in Ig A and Ig M levels (13). Ig M is an immunoglobulin derivative which is effective in defense against gram negative microorganisms. Ig M levels are elevated in these infections. There is a study in the literature which claims that Ig G, Ig M, C_3 and C_4 have no diagnostic value in early diagnosis (14). In our study, IgA and Ig G levels were normal in the study group before operation. While IgA did not show any significant increase in the control group during postoperative period, the increase in the study group was significant. In comparisons among the groups, there was not any difference with respect to increase. In Ig G levels, the control group did not show any change whereas a significant increase was observed in the study group postoperative 3rd and 7th days. Here also, no difference was observed in comparisons among the groups. Ig M levels showed increases in both groups during postoperative period, while in group comparisons, the increases observed in postoperative 1st, 3rd and 7th days in the study group were more significant ($p < 0.01$). CRP is a cell-originating substance with selective protein structure, and is secreted from inflamed cells, and starts to rise after 8- 10 hours following the

infection (15). Elevated levels may be observed after surgical traumas too (15), and normal levels are reached within postoperative 10th days (16). There are numerous studies related with the use of CRP in the diagnosis of acute appendicitis (17-21). It has also been reported that CRP series measurements in acute appendicitis may be employed as a parameter in the determination of postoperative injury infections and infectious complications (22). It is known that increases are observed in macrophage activation and in reactions containing local and systemic responses. However studies have shown that CRP alone has a poor sensitivity in the diagnosis of acute appendicitis (23). Despite this, it is still accepted that it reduces negative laparotomy rate. In our study, it was observed that serum CRP levels in the study group were significantly higher than in the control group (CRP $n < 3$ mg/L). While no change was observed in CRP levels in the control group during postoperative period, significant decreases were found in the study group during the same period following removal of infection source. In group comparisons, CRP levels in the study group were higher than the control group at all times.

It is known that serum leukocyte levels become elevated in infectious and inflammatory diseases, after surgical traumas and in sepsis. There are many studies reporting low specificity and high sensitivity rates related with the increase in the leukocyte number in acute appendicitis (17, 24-28). Although it is not a very sensitive method of diagnosis alone in complicated acute appendicitis, it is considered to be a more useful test when combined with other laboratory parameters. In our study, elevated leukocyte levels before the operation showed a progressive decrease, along with the clinical improvement observed after the operation (Table 2, $p < 0.05$). Contrary to this, it was observed that high serum leukocyte levels in the control group after the postoperative period. But this increase was not statistically significant ($p > 0.05$) and the values were within normal limits.

In conclusion, though anamnesis and examination findings have priority in the diagnosis of acute appendicitis, diagnosis is facilitated with the support of laboratory tests. To this end, examination of serum leukocyte, CRP, IG M and fibronectin levels will enhance the diagnosis. Lower serum fibronectin, higher CRP and leukocyte levels as well as lower IGM levels may provide preliminary findings for establishing an acute appendicitis diagnosis. Besides, the facts that no increase in serum fibronectin levels after the operation, no decrease in leukocyte levels and no increase in IG M levels during postoperative period may provide preliminary information with respect to development of septic source.

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Received: June 19, 2001

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