

Can Intestinal Fatty Acid Binding Protein (I-FABP) Be A Marker in the Diagnosis of Abdominal Pathology?

FABP'nin İntestinal Tipi (I-FABP) Abdominal Patolojilerin Tanısında Belirteç Olabilir mi?

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SUMMARY

Objectives

Biochemical markers play an important role in the early diagnosis of abdominal pain. This study aimed to investigate the diagnostic value of intestinal type fatty acid binding protein (I-FABP) in patients with abdominal pathology.

Methods

This prospective and descriptive study was performed at the University Hospital Emergency Department. Serum I-FABP levels of patients presenting with acute abdominal pain were measured at time of admission and were compared with those of healthy individuals.

Results

The mean I-FABP level of the 171 patients enrolled in this study was 170.1±543.4 pg/ml, while that of a healthy control group was 61.4±47.4 pg/ml. Although I-FABP levels were higher in the patient group, this difference was not statistically significant ($p>0.05$). However, I-FABP levels of patients with mesenteric ischemia and intra-abdominal mass were significantly higher than those of healthy individuals ($p<0.05$).

Conclusions

I-FABP levels that are evaluated at time of admission in patients presenting with abdominal pain to the emergency department are significantly higher in patients with mesenteric ischemia and intra-abdominal mass than are those of healthy individuals.

Key words: Abdominal mass; abdominal pain; I-FABP; mesenteric ischemia.

ÖZET

Amaç

Biyokimyasal belirteçler karın ağrısının sebebinin erken tanısında oldukça önemlidir. Bu çalışmada FABP'nin intestinal tipinin (I-FABP) abdominal patolojisi olan hastaların ayırıcı tanısındaki değeri araştırıldı.

Gereç ve Yöntem

Mevcut çalışma üniversite hastanesi acil servisinde ileriye yönelik tanımlayıcı olarak çalışma gerçekleştirildi. Karın ağrısı şikayeti ile acil servise başvuran hastalarda başvuru anında alınan serum örneklerinden I-FABP değerlerine bakıldı. Bulgular sağlıklı gönüllülerdeki düzeyler ile karşılaştırıldı.

Bulgular

Kayıtlı 171 hastada ölçülen ortalama I-FABP seviyesi 170.1±543.4 pg/ml olarak belirlendi. Sağlıklı gönüllülerde I-FABP seviyesi 61.4±47.4 pg/ml olarak bulundu. Hasta grubunun I-FABP seviyeleri sağlıklı gönüllülere göre yüksek olarak bulunmuşsa da, aradaki fark istatistiksel olarak anlamlı değildi ($p>0.05$). Başvuru anında ölçülen I-FABP seviyeleri sağlıklı gönüllülerle kıyaslandığında akut mezenter iskemide (AMI) ve karıniçi kitle tespit edilen hastalarda istatistiksel olarak anlamlı yüksekti ($p<0.05$).

Sonuç

Acil servise karın ağrısı şikayeti ile başvuran hastalardan mezenter iskemide ve karıniçi kitle tanısı alan hastalarda başvuru anında ölçülen serum I-FABP değerleri sağlıklı gönüllülere kıyaslandığında anlamlı olarak yüksek bulunmuştur.

Anahtar sözcükler: Karın ağrısı; batında kitle; I-FABP; mezenter iskemisi.

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Introduction

Biochemical markers can be easily obtained, are widely used, and are becoming very important in the early diagnosis of abdominal pathology. Specific biochemical markers have been reported for several pathologies, including alanine aminotransferase for hepatic injury and amylase for pancreatitis.^[1] Although several studies have been published regarding this issue, several abdominal pathologies have no specific biochemical markers. These previously published studies include investigations regarding the diagnostic and prognostic values of D-dimer, MMP-9, IMA, I-FABP, alpha glutathione S transferase, D-lactate and S100 A8/A9 levels in patients with abdominal pain.^[2-8]

Fatty acid binding protein (FABP) is a small (12-15 kDa) intracellular protein that increases in conditions such as inflammation and ischemia. It plays a role in protecting cells from the side effects of fatty acids and increases in association with various pharmacological and pathophysiological effects, such as ischemia.^[9] Several types of FABP have been described immunologically, including heart, intestinal, liver, epidermal, muscle and adipocyte. Intestinal FABP (I-FABP) is located exclusively in gastric epithelial cells and intestinal mucosa.^[10] Recently, Vermeulen et al. reported that I-FABP levels increase significantly due to intestinal ischemia after aortic surgery.^[11] Another study by Relja et al. showed that I-FABP and liver FABP (L-FABP) levels increase after abdominal trauma and are correlated with the severity of abdominal tissue injury in patients with polytrauma.^[12]

The purpose of this study was to compare I-FABP levels in patients admitted to the emergency department with abdominal pain and who were preliminarily diagnosed with abdominal pathology with I-FABP levels in a healthy control group. This study was based on the hypothesis that I-FABP may be a useful diagnostic marker in the differential diagnosis of abdominal pathology.

Materials and Methods

This prospective and descriptive study was performed with patients who presented to our University Hospital Emergency Department between June 2009 and June 2010 with abdominal pain and who were diagnosed with abdominal pathology by emergency physicians and general surgeons. Patients were diagnosed on the basis of physical examination, ultrasonography and computerized tomography. Patients with trauma (n=80), pain lasting longer than 48 hours (n=24), those who were younger than 18 years (n=46), those who were unavailable for monitoring (n=13) and those who declined to participate (n=23) were excluded from the study. The control group consisted of age and

gender matched healthy hospital employees with no history of abdominal pathology. Approval for this study was obtained from the Ethics Committee of Karadeniz Technical University, Turkey (2009-21). Patients enrolled in the study were registered using a form that included demographic data, written permission, and routine patient evaluation data such as histories, physical examination results, biochemical values and radiological results. Venous blood specimens (10 cc) were taken from patients who presented to the emergency department with abdominal pain in order to measure serum I-FABP levels. Serum specimens obtained by centrifugation at 3000 x g for 10 min were kept at -20°C for a maximum of 6 months. Serum I-FABP levels were measured simultaneously at the end of the collection process.

Human serum I-FABP levels from patients and healthy individuals were measured using a commercial ELISA (Enzyme-Linked Immunosorbent Assay kit; Hycult Biotech, the Netherlands) kit according to the manufacturer's instructions. Absorbance values were measured using a VERSA max tunable microplate reader (designed by Molecular Devices in California, USA) at a wavelength of 450 nm. Results were expressed as picograms/mL.

Data were analyzed using SPSS version 10.0. Standard deviations of means and percentage frequency distributions were used as descriptive statistics. Normal distributions were calculated using the Kolmogorov-Smirnov test for numeric data. Nonparametric data were analyzed using the Mann-Whitney U test. The chi-square test was used for analyzing nominal parameters.

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and optimal cut-off value of I-FABP in patients presenting with abdominal pain were calculated using a receiver operating curve (ROC) analysis. The ROC analysis was used to determine the causes of abdominal pain for which the mean I-FABP levels were higher than those in healthy individuals.

Results

Three hundred and one cases were enrolled in this study, with 130 in the control group and 171 in the patient group. The mean age of the patient group was 52±21 years (range: 18-92 years) and was 56±8 years for healthy individuals.

The mean I-FABP level in the 171 patients was 170.1±543.4 pg/ml and was 61.4±47.4 pg/ml in the 130 healthy volunteers. Although the I-FABP levels in the patient group were higher than those in the healthy individuals, this difference was not statistically significant (p>0.05).

Table 1. I-FABP values of patients admitted to the emergency department with abdominal pain at the time of presentation

Definitive Diagnosis (n)	I-FABP levels pg/ml
	(Mean±SD)
Nonspecific abdominal pain (n=51)	53.5±55.7
Appendicitis (n=11)	73.9±131.4
Gall bladder diseases (n=30)	290.8±708.5
Ileus-volvulus (n=17)	130.8±221.9
Pancreatitis (n=14)	112.1±167.1
Mesenteric ischemia (n=7)	708.6±669.1*
Ovarian diseases (n=6)	129.3±261.2
Mass (n=15)	387.4±1380.2*
Gastritis-peptic ulcer (n=2)	65.1±34.1
Urolithiasis nephrolithiasis (n=11)	40.7±32.1
Hernia (n=4)	76.6±97.3
Perforation (n=1)	438.1
Total Patient (n=171)	170.1±543.3
Control (n=130)	61.4±47.4

*p<0.05 for mean I-FABP levels between the patient and control groups.

The patients were definitively diagnosed as follows: 11 (6.4%) with appendicitis, 30 (17.5%) with gall bladder diseases, 17 (9.9%) with ileus-volvulus, 14 (8.2%) with pancreatitis, 7 (4.1%) with mesenteric ischemia, 6 (3.5%) with

ovarian diseases, 15 (8.8%) with intra-abdominal mass, 2 (1.2%) with gastritis-peptic ulcer, 11 (6.4%) with nephrolithiasis-urolithiasis, 4 (2.3%) with herniation, 1 (0.6%) with perforation and 51 (29.8%) with non-specific abdominal pain.

The patients' I-FABP levels were expressed as groups and subgroups (Table 1). The average values for the acute mesenteric ischemia group and the intra-abdominal mass group were 708.6±669.1 pg/ml and 387.4±1380.2 pg/ml, respectively.

Our results show that the mesenteric ischemia and intra-abdominal mass patients were the only patients whose I-FABP levels were significantly higher than those of the healthy individuals. In addition, the I-FABP levels of the mesenteric ischemia patients were significantly higher than those of the mass patients. I-FABP sensitivity, specificity and ROC curves for NPV and PPV values were determined for these 2 diseases, and these data are shown in Figures 1 and 2.

The optimum cut-off I-FABP levels for the mesenteric ischemia and intra-abdominal mass patients according to ROC analysis as well as the sensitivity, specificity, NPV and PPV values for these levels are shown in Table 2.

The mean I-FABP level of the 49 patients who underwent surgery was 173.54387 pg/ml, and that of the 122 patients who did not undergo surgery was 168.6516 pg/ml. The difference between these values was not statistically significant (p>0.05).

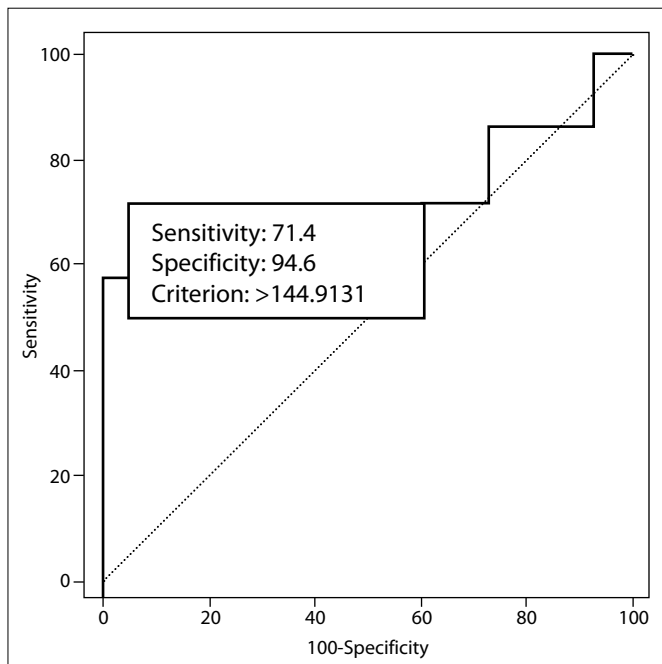


Figure 1. ROC curve of I-FABP values showing cut-off value, sensitivity, and specificity for mesenteric ischemia patients.

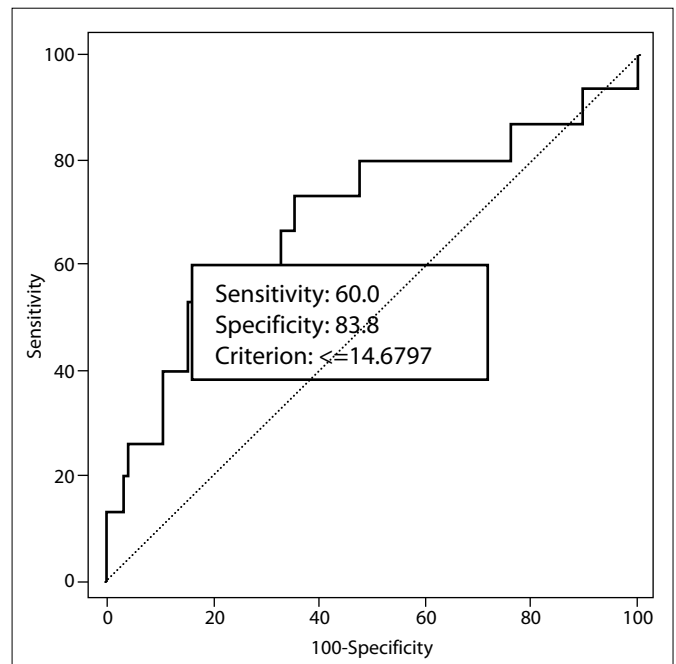


Figure 2. ROC curve of I-FABP values showing cut-off value, sensitivity, and specificity for mass patients.

Table 2. Sensitivity, specificity, PPV and NPV values for patients with mesenteric ischemia and mass

	AUC	Cut-off	Sensitivity	Specificity	PPV	NPV
For mesenteric ischemia	0.755	144.9	71.4	94.6	41.7	98.4
For mass	0.695	14.7	60.0	83.8	30.0	94.8

Discussion

Abdominal pain can be simple, but it may also be associated with life-threatening pathology. The early diagnosis of acute abdominal pain in the emergency department is highly important, especially for pathologies that may require surgical intervention. The most common etiological causes of abdominal pain are appendicitis, cholecystitis, small bowel obstruction, urinary colic, peptic ulcer perforation, pancreatitis and diverticulitis.^[13] In their review of abdominal pain, Grundmann et al.^[14] reported that the most frequent cause of acute abdominal pain was nonspecific abdominal pathology (24%-44.3%), followed by appendicitis (15.9%-28.1%) and biliary disease (2.9%-9.7%). Similarly, the most common cause of acute abdominal pain in our study was nonspecific abdominal pathology (29.8%), followed by gall bladder diseases (17.5%), ileus-volvulus (9.9%), intra-abdominal mass (8.8%), acute pancreatitis (8.2%), acute appendicitis (6.4%) and mesenteric ischemia (4.1%). The breakdown of patient groups in our study may be different from those previously published because our study was performed in a tertiary teaching and research hospital that works in co-ordination with other institutions.

Both clinical findings and laboratory tests are often used for diagnosing acute abdomen. White blood cell (WBC) count is an important and oft-used laboratory parameter,^[15] and D-dimer is frequently used in the evaluation of patients with acute abdominal pain.^[1,16] Studies have reported that MMP-9 levels are increased in patients with ureteral stones, acute cholecystitis and intestinal obstructions.^[4] Significantly elevated ischemia modified albumin (IMA) levels have also been reported in mesenteric ischemia models.^[5] Several recent reviews have indicated that the most optimistic plasma biomarkers are I-FABP, alpha-glutathione S-transferase and D-lactate. I-FABP and alpha-glutathione S-transferase are localized in the mucosa of the small intestine. Since intestinal injury during acute mesenteric ischemia begins at the intestinal mucosa, these markers can potentially be used in the early phase.^[17] In addition, I-FABP, alpha-glutathione S-transferase and CK-MB levels differed significantly from the control group in a suspected acute mesentery ischemia population. Serum phosphate level has also been investigated for the diagnosis of acute mesentery ischemia. Clinical and experimental studies have shown that the increase in serum

phosphate levels in acute mesentery ischemia develops following ischemia-related intestinal necrosis and widespread cell death. Therefore, elevated serum phosphate is not a suitable marker for the early diagnosis of acute mesentery ischemia. However, it can be used as a prognostic indicator as well as an indicator of irreversible intestinal necrosis.^[18,19]

Evennett et al.^[1] reported that the most reliable plasma markers for intestinal ischemia are I-FABP, which is present in the mucosa of the small intestine, alpha-glutathione S-transferase, and D-lactate, which is released from bacteria in the intestinal lumen as a product of bacterial fermentation. Another study showed that an alpha-glutathione S-transferase level <4 ng/ml has a 100% negative predictive value in eliminating ischemic intestinal disease. The same study also showed that the increase in alpha GST levels had a negative predictive value of 92% in patients with suspected acute mesentery ischemia.^[6] Bealer et al.^[7] determined a diagnostic value of S100A8/A9 (calgranulin A/B) with 93% sensitivity and 54% specificity in patients with suspected acute appendicitis.

In a clinical study investigating the use of I-FABP as a marker in acute abdomen cases, Kanda et al.^[20-22] enrolled a total of 96 individuals. Of these, 13 were diagnosed pre-surgically with ischemic intestinal disease (5 cases of mesenteric ischemia and 8 of strangulated hernia), 48 had a diagnosis of acute abdomen, and 35 served as healthy controls. This study also reported significantly high I-FABP values (>100 ng/mL) in 5 cases with mesenteric ischemia.

Tölle et al.^[23] reported elevated B-FABP in renal cell carcinoma patients and recommended that wider series be investigated to determine whether B-FABP could act as a tumor marker. Abdominal mass may cause ischemia, inflammation and intestinal membrane cell destruction, which do not typically lead to elevated FABP. These secondary causes may be assistant factors in these proteins being released into serum.

In our study with 171 patients and 130 healthy controls, the mean I-FABP levels were 170 pg/ml in the patient group and 61 pg/ml in the control group. Although there was a considerable numerical difference between these two means, this difference was not significant. Among the abdominal pathologies included in our study, I-FABP levels were only sig-

nificantly higher in patients with acute mesenteric ischemia and intra-abdominal mass when compared with the control group. However, there were no significant differences between I-FABP values among subgroups ($p>0.05$).

Conclusions

Although average I-FABP levels of patients presenting to the emergency department with abdominal pain at the time of admission were higher than those of the healthy individuals, this difference was not statistically significant. Serum I-FABP levels of patients presenting with abdominal pain and diagnosed with mesenteric ischemia and intra-abdominal mass were significantly higher when compared to those of the healthy volunteers. Therefore, I-FABP levels may be used to diagnose such fatal pathologies. Further studies with wider series are needed in order to investigate the diagnostic value of I-FABP in patients with abdominal pain.

Limitation

The very low patient numbers in some of the subgroups made it impossible to obtain reliable statistical data. Therefore, I-FABP should be investigated in wider study groups.

Conflict of Interest

The authors declare that there is no potential conflicts of interest.

References

- Evennett NJ, Petrov MS, Mittal A, Windsor JA. Systematic review and pooled estimates for the diagnostic accuracy of serological markers for intestinal ischemia. *World J Surg* 2009;33:1374-83. [CrossRef](#)
- Acosta S, Nilsson TK, Björck M. D-dimer testing in patients with suspected acute thromboembolic occlusion of the superior mesenteric artery. *Br J Surg* 2004;91:991-4. [CrossRef](#)
- Acosta S, Nilsson TK, Björck M. Preliminary study of D-dimer as a possible marker of acute bowel ischaemia. *Br J Surg* 2001;88:385-8. [CrossRef](#)
- Solberg A, Holmdahl L, Falk P, Palmgren I, Ivarsson ML. A local imbalance between MMP and TIMP may have an implication on the severity and course of appendicitis. *Int J Colorectal Dis* 2008;23:611-8. [CrossRef](#)
- Gunduz A, Turkmen S, Turedi S, Mentese A, Yulug E, Ulusoy H, et al. Time-dependent variations in ischemia-modified albumin levels in mesenteric ischemia. *Acad Emerg Med* 2009;16:539-43. [CrossRef](#)
- Delaney CP, O'Neill S, Manning F, Fitzpatrick JM, Gorey TF. Plasma concentrations of glutathione S-transferase isoenzyme are raised in patients with intestinal ischaemia. *Br J Surg* 1999;86:1349-53. [CrossRef](#)
- Bealer JF, Colgin M. S100A8/A9: a potential new diagnostic aid for acute appendicitis. *Acad Emerg Med* 2010;17:333-6.
- Acosta S, Nilsson T. Current status on plasma biomarkers for acute mesenteric ischemia. *J Thromb Thrombolysis* 2012;33:355-61. [CrossRef](#)
- Niewold TA, Meinen M, van der Meulen J. Plasma intestinal fatty acid binding protein (I-FABP) concentrations increase following intestinal ischemia in pigs. *Res Vet Sci* 2004;77:89-91.
- Glatz JF, van der Vusse GJ. Cellular fatty acid-binding proteins: their function and physiological significance. *Prog Lipid Res* 1996;35:243-82. [CrossRef](#)
- Vermeulen Windsant IC, Hellenthal FA, Derikx JP, Prins MH, Buurman WA, et al. Circulating intestinal fatty acid-binding protein as an early marker of intestinal necrosis after aortic surgery: a prospective observational cohort study. *Ann Surg* 2012;255:796-803. [CrossRef](#)
- Relja B, Szermutzky M, Henrich D, Maier M, de Haan JJ, Lubbers T, et al. Intestinal-FABP and liver-FABP: Novel markers for severe abdominal injury. *Acad Emerg Med* 2010;17:729-35.
- Parker LJ, Vukov LF, Wollan PC. Emergency department evaluation of geriatric patients with acute cholecystitis. *Acad Emerg Med* 1997;4:51-5. [CrossRef](#)
- Grundmann RT, Petersen M, Lippert H, Meyer F. The acute (surgical) abdomen - epidemiology, diagnosis and general principles of management. [Article in German] *Z Gastroenterol* 2010;48:696-706. [Abstract] [CrossRef](#)
- Silen W. Abdominal pain. Harrison's principles of internal medicine. 15th ed. Vol. I. 1998.
- Akyildiz HY, Sözüer E, Akcan A, Küçük C, Artis T, Biri I, et al. The value of D-dimer test in the diagnosis of patients with nontraumatic acute abdomen. *Ulus Travma Acil Cerrahi Derg* 2010;16:22-6.
- Ockner RK, Manning JA. Fatty acid-binding protein in small intestine. Identification, isolation, and evidence for its role in cellular fatty acid transport. *J Clin Invest* 1974;54:326-38. [CrossRef](#)
- Lores ME, Cañizares O, Rosselló PJ. The significance of elevation of serum phosphate levels in experimental intestinal ischemia. *Surg Gynecol Obstet* 1981;152:593-6.
- Chen Y, Milles AM, Grisham BM. Pathophysiology and reactive oxygen metabolites. Oxidative stress and antioxidant defenses in biology. 1st ed. New York: Chapman and Hall Co; 1995. p. 62-95. [CrossRef](#)
- Kanda T, Fujii H, Tani T, Murakami H, Suda T, Sakai Y, et al. Intestinal fatty acid-binding protein is a useful diagnostic marker for mesenteric infarction in humans. *Gastroenterology* 1996;110:339-43. [CrossRef](#)
- Kanda T, Nakatomi Y, Ishikawa H, Hitomi M, Matsubara Y, Ono T, et al. Intestinal fatty acid-binding protein as a sensitive marker of intestinal ischemia. *Dig Dis Sci* 1992;37:1362-7. [CrossRef](#)
- Kanda T, Fujii H, Fujita M, Sakai Y, Ono T, Hatakeyama K. Intestinal fatty acid binding protein is available for diagnosis of intestinal ischaemia: immunochemical analysis of two patients with ischaemic intestinal diseases. *Gut* 1995;36:788-91. [CrossRef](#)
- Tölle A, Jung M, Lein M, Johannsen M, Miller K, Moch H, et al. Brain-type and liver-type fatty acid-binding proteins: new tumor markers for renal cancer? *BMC Cancer* 2009;9:248. [CrossRef](#)