

## CLINICAL STUDY

## Serum Ykl-40 levels in acute appendicitis

Koc M<sup>1</sup>, Zulfikaroglu B<sup>1</sup>, Kemal Isman F<sup>2</sup>, Ozalp N<sup>1</sup>, Acar A<sup>1</sup>, Kucur M<sup>3</sup>

Fifth Department of General Surgery, Ankara Numune Training and Research Hospital, Ankara, Turkey.  
mesuttez@yahoo.com

**Introduction:** Acute appendicitis is one of the most common abdominal emergencies. The clinical diagnosis is often difficult even for experienced surgeons, however, as evidenced by the high rate of negative explorations. A delay in diagnosis of acute appendicitis is associated with increased risk of perforation and further complications.

**The aim** of the present study was to assess the preoperative YKL-40 levels on for a clinical suspicion of acute appendicitis.

**Methods:** Between August 2008 and December 2008, a total of 34 patients who underwent appendectomy with a clinical diagnosis of acute appendicitis were studied. Patients underwent appendectomy with the preoperative diagnosis of acute appendicitis. The appendix specimens were classified as normal appendix (group 1; 10 patients), acute appendicitis (group 2; 24 patients). Serum YKL-40 levels were determined by a commercial ELISA.

**Results:** The levels of serum YKL-40 were significantly higher in the group 2 compared with the group 1 ( $66.4 \pm 13.2$  vs  $41.6 \pm 11.6$  ng/mL,  $p < 0.001$ ). Receiver operating characteristic curves of YKL-40 levels counts was on a statistically significant level (area under the curve [AUC] = 0.926,  $p < 0.001$ )

**Conclusion:** YKL-40 may be a useful marker for diagnosis of acute appendicitis but the number of subjects was limited in this study, future studies are required to confirm the results presented here (Fig. 1, Ref. 13). Full Text in free PDF [www.bmj.sk](http://www.bmj.sk).

**Key words:** YKL-40, acute appendicitis, inflammation.

KL-40 (also named chitinase-3-like-1 (CHI3L1) and human cartilage glycoprotein-39 (HC-gp39)) is a 40 kDa heparin-, chitin- and collagen-binding phylogenetically highly conserved glycoprotein. It is a member of 'mammalian chitinase-like proteins', but has no chitinase activity. The YKL-40 protein contains a single polypeptide chain of 383 amino acids and has a molecular mass of 40 kDa (1).

YKL-40 can be regarded as an acute phase protein, since its plasma concentration increases in patients by more than 25 % following an inflammatory stimulus. Serum or plasma concentrations of YKL-40 are often elevated, compared to healthy subjects, in patients with diseases characterized by inflammation, increased extracellular remodeling or ongoing fibrosis such as infections (2).

Acute appendicitis (AA) is one of the most common abdominal emergencies. The clinical diagnosis is often difficult even for experienced surgeons, however, as evidenced by the high rate of negative explorations, which commonly reaches 20 % to 30 % (3). Many attempts have been made to determine ways of decreasing the negative laparotomy rate after a clinical suspicion of AA. However, despite complete clinical history, physical ex-

amination, and the usual laboratory studies, clear decision aids for detection of early AA are lacking. Laboratory measurements such as WBC count, neutrophil percentage, and C-reactive protein (CRP) concentration are commonly used as diagnostic aids in patients with suspected acute appendicitis(3).

However, there is little information about the diagnostic value of serum YKL-40 levels in AA.

The aim of the present study was to evaluate the diagnostic importance of the preoperative YKL-40 levels in acute appendicitis.

## Material and methods

### Patients

Between August 2008 and December 2008, a total of 34 patients underwent appendectomy with a clinical diagnosis of acute appendicitis at the Emergency Department, Ankara Numune Training and Research Hospital. The clinical diagnosis was established preoperatively by clinical history, physical examination, and laboratory tests including WBC count and neutrophil percentage. Demographic, surgical, and histopathologic variables were recorded retrospectively. Patients underwent appendectomy with the preoperative diagnosis of acute appendicitis. Removed appendices were fixed in formalin and analyzed histologically. The appendix specimens were classified as normal appendix, acute appendicitis.

This study was approved by the medical ethics committee of the Ankara Numune Training and Research Hospital. All subjects signed consent forms.

<sup>1</sup>Fifth Department of General Surgery, Ankara Numune Training and Research Hospital, Ankara, Turkey, <sup>2</sup>Department of Clinical Chemistry, Taksim Teaching and Research Hospital, İstanbul, and <sup>3</sup>Department of Biochemistry, Fikret Biyal Central Research Laboratory, Cerrahpasa School of Medicine, İstanbul University, Turkey

**Address for correspondence:** M. Koç, Fifth Department of General Surgery, Ankara Numune Training and Research Hospital, Ankara, Turkey. Phone: +90.312.2153834, Fax: +90.312.3103460

### Biochemical analysis

Blood samples were left on the clot, and serum was separated from cellular elements by centrifugation within two hours after blood sampling. All serum samples were stored at  $-20^{\circ}\text{C}$  until analysis. Serum YKL-40 concentrations were determined by a commercial ELISA (Quidel Corporation, Santa Clara, CA) (24). The intra- and inter-assay variations were 3.6 % and 5.3 %, respectively. The sensitivity of the assay was 20 ng/mL.

### Statistical analysis

The data were expressed as mean  $\pm$  SD. Statistical analysis was carried out using SPSS 11.0 for Windows (SPSS Inc, Chicago, Ill). The differences between the group 1 and the group 2 were estimated using the Chi-square (for gender distribution) and two-tailed unpaired t-test (for normally distributed data). Mann-Whitney-U test was used to evaluate YKL-40 levels in studied groups. We measured the clinical performance of YKL-40 levels using receiver operating characteristic (ROC) curves and calculated likelihood ratios for 2 cut-points with either high sensitivity or high specificity.

A p value of  $< 0.05$  was considered to be statistically significant.

### Results

A total of 34 patients were included in this study of whom 10 had a normal appendix histopathologically (Group 1), giving an overall negative appendectomy rate of 29.4 %. In this study, 23 (67 %) patients were males and 11 (33 %) were females, the male to female ratio being 2:1. The age range was 16 – 72 years, with a median age of 28.1 years.

Among the 34 patients 24 had an inflamed appendix (Group 2).

The levels of serum YKL-40 were significantly higher in the group 2 compared with the group 1 ( $66.4 \pm 13.2$  vs  $41.6 \pm 11.6$  ng/mL,  $p < 0.001$ ).

Receiver operating characteristic curves of YKL-40 levels counts were used to identify patients with appendicitis (group 1 vs 2) on a statistically significant level (area under the curve [AUC] = 0.926,  $p < 0.001$ ) (Fig. 1).

### Discussion

In the present study serum YKL-40 levels were measured to assess its usefulness as inflammatory markers in the etiology of acute appendicitis. To the best of our knowledge, this is the first study to show increased YKL-40 levels in patients with acute appendicitis.

Although the incidence of acute appendicitis appears to have been increasing slightly over the past few decades, it remains a frequent cause of acute abdominal pain and urgent operative intervention. If untreated, acute appendicitis will progress from inflammation to perforation with abscess formation or diffuse peritonitis, making timely operative intervention imperative. Generally, the morbidity and mortality of missing a case of acute appendicitis with subsequent peritonitis or abscess formation far

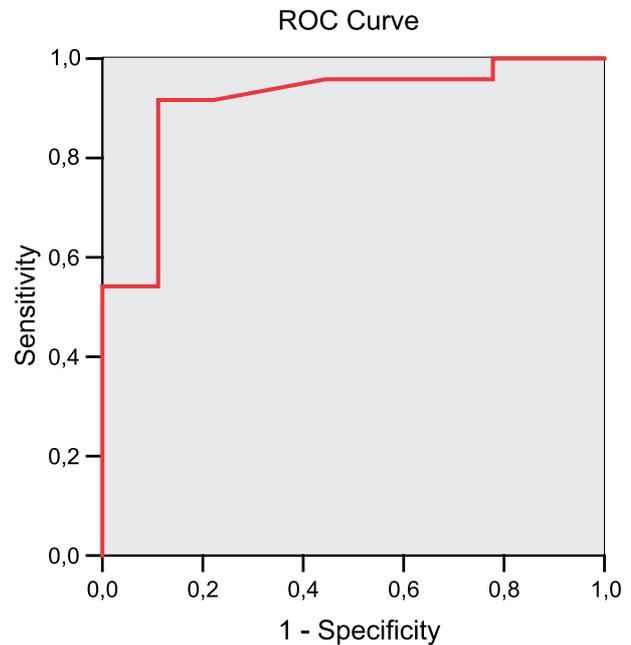


Fig. 1. Receiver operating characteristic curves of YKL-40 levels.

outweigh the complications associated with a negative appendectomy (5).

The analysis of a patient with possible appendicitis can be divided into 3 parts: history, physical examination, and routine laboratory and x-ray tests. The leukocyte count is the test probably most often used to diagnose acute appendicitis. Several reports suggest that an elevated leukocyte count is usually the earliest laboratory test to indicate appendiceal inflammation, and most of the patients with acute appendicitis present with leukocytosis (5). Both leukocyte count and neutrophil percentage are not specific for acute appendicitis. Therefore, surgeons still have difficulty in diagnosing appendicitis accurately, and controversy exists regarding the relative usefulness of laboratory tests in the diagnosis of acute appendicitis. Leukocytosis is a nonspecific reaction caused by acute or chronic inflammation, acute physical or emotional stress, and several other conditions. This is reflected in numerous reports by an acceptable sensitivity (79 – 93 %) but a rather low specificity for AA (6).

C-reactive protein is also an important serum inflammatory marker in the diagnosis of appendicitis in the pediatric age group. After 6 to 12 hours of inflammation, the concentration begins to rise and may increase a hundredfold (7). However, in a meta-analysis, CRP has been shown to have a medium sensitivity (53 – 88 %) and specificity (46 – 82 %) for appendicitis (8).

IL-6, IL-8, and soluble adhesion molecule CD 44, CRP, and white blood cell count to predict AA. Among these parameters IL-6 was elevated preoperatively only in gangrenous and perforated AA, and showed the best diagnostic accuracy in predicting AA (9).

Recent clinical studies have reported that YKL-40 is expressed in pathological conditions, and it has been evaluated as a prognostic serum marker of morbidity and mortality in some

diseases, including infections, some cancers and spinal disorders (1, 2, 10, 11) since the pattern of its elevation in normal and disease states suggests that YKL-40 plays an important role in inflammatory processes, remodeling of the extracellular matrix and development of fibrosis. Thus, it seems that YKL-40 will be used as a marker for inflammation in routine clinical practice in the near future and may replace CRP (12). Serum levels of YKL-40 are elevated in patients with purulent meningitis (1) and pneumonia (1) as well as in patients with endotoxemia caused by injection of *E. coli* endotoxin (13). In both meningitis and pneumonia, YKL-40 is secreted by locally activated macrophages and neutrophils and is released by exocytosis from specific granules at the site of inflammation, when needed for bactericidal activity (1). Because of this local production, YKL-40 levels show a more rapid peak and a more rapid decline after initiation of antibiotic treatment, which is opposite to CRP levels that decline slowly (1). Opposite to YKL-40, CRP is primarily a systemic inflammation marker secreted by hepatocytes in response to proinflammatory mediators such as IL-6.

In conclusion; YKL-40 may be a useful marker for diagnosis of acute appendicitis but the number of subjects were limited in this study, future studies are required to confirm the results presented here.

## References

1. Roslind A, Johansen JS. YKL-40: a novel marker shared by chronic inflammation and oncogenic transformation. *Methods Mol Biol* 2009; 511: 159–184.
2. Nordenbaek C, Johansen JS, Junker P, Bor-Regaard N, Sørensen O, Price PA. YKL-40, a matrix protein of specific granules in neutrophils, is elevated in serum of patients with community-acquired pneumonia requiring hospitalization. *J Infect Dis* 1999; 180: 1722–1726.
3. Kronborg G, Røstergaard C, Weis N, Nielsen H, Obel N, Pedersen SS et al. Serum level of YKL-40 is elevated in patients with *Streptococcus pneumoniae* bacteremia and is associated with the outcome of the disease. *Scand J Infect Dis* 2002; 34: 323–326.
4. Yang HR, Wang YC, Chung PK, Chen WK, Jeng LB, Chen RJ. Laboratory tests in patients with acute appendicitis. *ANZ J Surg* 2006; 76: 71–77.
5. Keskek M, Tez M, Yoldas O, Acar A, Akgul O, Gocmen E, Koc M. Receiver operating characteristic analysis of leukocyte counts in operations for suspected appendicitis. *Am J Emerg Med* 2008; 26: 769–772.
6. Hallan S, Asberg A, Edna TH. Additional value of biochemical tests in suspected acute appendicitis. *Eur J Surg* 1997; 163: 533–538.
7. Peltola H, Ahlqvist J, Rapola J, Rasanen J, Louhimo I, Saarinen M. C-reactive protein compared with white blood cell count and erythrocyte sedimentation rate in the diagnosis of acute appendicitis in children. *Acta Chir Scand* 1986; 152: 55–58.
8. Hallan S, Asberg A. The accuracy of C-reactive protein in diagnosing acute appendicitis—a meta-analysis. *Scand J Clin Lab Invest* 1997; 57: 373–380.
9. Sack U, Biereder B, Elouahidi T, Bauer K, Keller T, Tröbs RB. Diagnostic value of blood inflammatory markers for detection of acute appendicitis in children. *BMC Surg* 2006; 6: 15.
10. Tanwar MK, Gilbert MR, Holland EC. Gene expression microarray analysis reveals YKL-40 to be potential serum marker for malignant character in human glioma. *Cancer Res* 2002; 62: 4364–4368.
11. Tsuji T, Matsuyama Y, Natsume N et al. Analysis of chondrex (YKL-40, HC gp-39) in the cerebrospinal fluid of patients with spine disease. *Spine* 2002; 27: 732–735.
12. Kacira T, Hanimoglu H, Kucur M, Sanus GZ, Kafadar AM, Tanriverdi T, Kaynar MY. Elevated cerebrospinal fluid and serum YKL-40 levels are not associated with symptomatic vasospasm in patients with aneurysmal subarachnoid haemorrhage. *J Clin Neurosci* 2008; 15: 1011–1016.
13. Johansen JS, Krabbe KS, Møller K, Pedersen BK. Circulating YKL-40 levels during human endotoxaemia. *Clin Exp Immunol* 2005; 140: 343–348.

Received August 24, 2009.  
Accepted September 20, 2010.