Role of serum levels of tumour necrosis factor-like weak inducer of apoptosis (TWEAK) in predicting severity of acute appendicitis

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ABSTRACT

Objective: One of the most prevalent abdominal crises is acute appendicitis (AA). Clinical diagnosis, even for skilled surgeons, is frequently challenging, as indicated by the high proportion of negative investigations. The purpose of this study was to see if serum TWEAK levels might be used to diagnose acute appendicitis.

Material and Methods: Between June 2017 and May 2019, all patients who had surgery with the original diagnosis of AA were included in the study. TWEAK, WBC, CRP, and bilirubin levels were compared.

Results: The levels of WBC, CRP, and bilirubin were compared to pathology. All three blood indicators increased significantly in AA patients. However, no statistically significant difference in the levels of all three blood indicators was seen between individuals with simple AA and those with severe AA. TWEAK plasma concentrations were considerably greater in patients with severe AA than in the healthy control and NAA groups. TWEAK levels were significantly greater in individuals with severe AA compared to patients with simple AA.

Conclusion: Serum TWEAK levels that are elevated may be used to diagnose acute appendicitis as well as prognostic indicators for the severity of appendicitis.

Keywords: Acute appendicitis, inflammation, marker, severity, tumor necrosis factor-like weak inducer of apoptosis

INTRODUCTION

One of the most prevalent abdominal crises is acute appendicitis (AA). Clinical diagnosis is sometimes challenging, even for experienced surgeons, as indicated by the high percentage of negative explorations, which typically approaches 20-30% (1,2). Acute appendicitis is mostly a clinical diagnosis backed by laboratory and imaging tests. Despite the introduction of various clinical scoring systems, their accuracy remains modest and comparable to traditional clinical judgment. Modern imaging may improve diagnostic accuracy, but its usage may be restricted by availability, cost, and radiation exposure. Difficulties in diagnosing acute appendicitis have led to an ongoing search for new diagnostic indicators that may reduce radiation exposure and expenditures (3-6). Patient outcomes are frequently favorable with early identification and correct therapy. However, delayed detection can lead to perforation, which can result in serious consequences such as peritonitis, sepsis, intestinal blockage, abscess development, and reproductive issues. Perforated appendicitis has been demonstrated to significantly increase mortality. However, clinicians must strike a balance between attempts to decrease delayed/missed diagnoses and over-diagnosis, which results in unnecessary treatments (medical/surgical) (7,8).

Chicheportich identified tumor necrosis factor-like weak inducer of apoptosis (TWEAK) as a novel member of the tumor necrosis factor (TNF) superfamily of ligands in 1997. TWEAK has been shown in studies to be a valuable biomarker in a variety of inflammatory and non-inflammatory illnesses (9). In recent decades, there has been a significant increase in the literature regarding the use of TNF inhibitors in the treatment of BD. Therefore, TWEAK has been the focus of attention in current studies (9). TWEAK is a cytokine that is mostly generated by leukocytes and is a

member of the TNF family. Furthermore, disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis are caused by cellular responses that can be linked to inflammatory pathways triggered by inflammatory multifunctional cytokines like TWEAK (9). TWEAK may have an important role in the pathological remodeling underlying various inflammatory disorders, such as cardiovascular disease and obesity-associated type 2 diabetes mellitus, notably in myocardial remodeling leading to heart failure and acute pancreatitis, according to new data (9).

Therefore, the aim of the present study was to test the diagnostic value of serum levels of TWEAK in acute appendicitis.

MATERIAL and METHODS

All patients who were operated to surgical emergency department with the initial diagnosis of acute appendicitis, were included prospectively between June 2017 and May 2019.

Written, informed consent was obtained according to a protocol approved by local institutional ethical committee. Patients with age <18 years, other acute infections, malignant disease, chronic inflammatory disease (including established or suspected chronic pancreatitis), preexisting chronic organ failure, unstable coronary syndromes, liver failure, chronic obstructive airways disease, and immunosuppressive disorders were excluded due to potential variations in the systemic inflammatory responses and their potential influence on treatment decisions.

After informed consent, routine laboratory studies were obtained in all patients, together with complete blood count and serum chemistry analysis, including CRP levels from the admission blood sample.

All blood specimens were immediately processed after they were drawn and stored in aliquots at -80°C till quantification of sTWEAK.

Serum sTWEAK levels were determined with a commercially available ELISA kit tested for determination of human serum samples (Bender Medsystems, Wien, Austria) according to the manufacturer's instructions. Briefly, a 1:2 diluted test sample was incubated for three hrs at room temperature in wells pre-coated with an anti-human sTWEAK antibody together with a biotin-conjugated anti-human TWEAK antibody. Streptavidin-HRP (horse reddish peroxidase) binds to the biotin-conjugated anti-human TWEAK. Following incubation, wells were washed three times to remove excess antibody, the substrate solution reactive with HRP was added to the wells and incubated for approximately 10-20 min. A colored product is formed in proportion to the amount of soluble human TWEAK present in the sample. The reaction was terminatedby addition of acid and absorbance was measured at 450 nm. A standard curve prepared from seven human TWEAK standard dilutions and subsequently human TWEAK sample concentrations were determined. The absorbance was measured with an automatic

ELISA reader (Biochem Immunosystems 100 Cascade Drive, Allentown, PA). Human sTWEAK was detected with this kit at a threshold of 9.7 pg/mL. Intra-assay and inter-assay coefficients of variation were 7.9% and 9.2%, respectively.

All measurements were performed in duplicate.

Data regarding demographic, clinical, radiological, operative, and pathological features were analyzed. The severity of appendicitis, as described in histological examination, was classified as normal (not acute appendicitis, NAA), simple appendicitis, severe appendicitis (in cases of acute appendicitis with periappendicitis or phlegmonous/gangrenous or perforated appendix) similar to the pathologic classification described by Fallon and colleagues (3).

Findings of each marker for overall acute appendicitis, and severe appendicitis were compared to histological findings using the following definitions: sensitivity, (true positive/true positive + false negative); specificity, (true negative/true negative + false positive); positive predictive value, (PPV) (true positive/true positive + false positive); and negative predictive value (NPV), (true negative/true negative ++ false negative).

The receiver operating characteristic (ROC) analysis allows graphical plotting of the sensitivity vs. specify curve to assess the overall performance of the parameter as a diagnostic factor [area under the curve (AUC)] and discern the optimal threshold value. ROC curve analysis was performed for all evaluated. The statistically significant variables were inspected for a cutoff value for optimal diagnostic accuracy [calculated as (true positive + true negative)/N]. Negative and positive predictive values (NPV, PPV) were calculated and recorded. Study population was grouped using the selected variable cutoffs and diagnostic accuracy of overall appendicitis, and severe appendicitis was assessed using Fisher's exact test. Correlation of the variables to the severity of appendicitis, according to operative and pathological reports, was assessed using Spearman's correlation test.

The data were expressed as mean ± SD and 95% confidence interval (CI). Statistical analysis was carried out using SPSS 11.0 for Windows (SPSS Inc, Chicago, IL). The differences between the groups 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 serum TWEAK levels in studied groups. A p value of <0.05 was considered to be statistically significant.

RESULTS

The study protocol included 200 patients who underwent operations with diagnosis of AA; all met the eligibility criteria, as well as 50 healthy volunteers. According to the surgery and pathology reports, 168 acute appendicitis (simple & severe AA) and 82 (NAA & control) normal people were detected, respectively. According to the pathology reports, 104 simple AA and 64 severe AA patients were detected. The demographics and clini-

cal presentation are summarized in Table 1. Male gender had a higher rate of acute appendicitis (p< 0.05). While 72 (69.23%) uncomplicated cases and 39 (60.93%) severe appendicitis cases were male, 23 (71.88%) non-appendicitis cases were female.

WBC, CRP and bilirubin levels were compared to pathology. In comparison to the NAA and control groups, all three blood markers increased significantly in patients with simple and severe AA (Table 2). On the other hand, when we compared the levels of all three blood markers between patients with simple and severe appendicitis, there was no statistically significant difference (p= 0.89, p= 0.63, and p= 0.21, respectively).

As shown in Table 2, the mean plasma concentration of TWEAK in patients with severe AA was 945.6 ± 121.2 pg/mL (95% CI 798.93-997.07), significantly higher than that of the healthy control group 385.2 ± 62.9 pg/mL and NAA group 391.7±67.7 pg/mL (p≤0.001). The mean level in simple AA patients (635.4 ± 107.1 pg/mL) (95% CI 541.84-694.25) was also notably higher than that of healthy volunteers and NAA group. Importantly, significantly higher levels of TWEAK were detected in patients with severe AA compared to simple AA.

A correlation was analyzed between the studied markers and the acute appendicitis as recorded in operative and pathology reports. Serum TWEAK levels had the significant sensitivity, specificity, PPV and NPV (Table 3).

Table 1. Comparison of demographics and clinical presentation

	NAA (n= 32)	Simple AA (n= 104)	Severe AA (n= 64)	Control (n= 50)	p
Age	34.3 ± 8.7	32.1 ± 7.8	35.7 ± 8.2	32.3 ± 7.3	0.61
Male sex, n (%)	9 (28.12%)*	72 (69.23%)*	39 (60.93%)*	26 (52%)	0.04*
Duration of symptoms (hours)	33.4 ± 4.7	25.2 ± 4.2	37.0 ± 0.6		0.43
Maximal fever (ºC)	36.8 ± 0.6	37.0 ± 0.7	37.0 ± 0.6	36.7 ± 0.6	0.87
Nauseai, n (%)	19 (59.37%)	67 (64.42%)	38 (59.37%)		0.48
Vomiting, n (%)	16 (50%)	55 (52.88%)	35 (54.68%)		0.38

t-NAA: Not acute appendicitis (normal), Simple AA: Simple appendicitis, Severe AA: Severe appendicitis.
Data are presented as mean ± SD.
(*): Statistically significant difference (p≤ 0.05).

Table 2. Comparison of laboratory findings

	NAA	Simple AA	Severe AA	Control	p
White blood cell count: x10^9/L	11.9 ± 4.5	14.2 ± 3.6*	14.6 ± 3.6*	7.2 ± 1.4	0.04*
CRP: mg/L	9.8 ± 2.2	12.4 ± 2.4*	14.1 ± 2.5*	4.2 ± 2.2	0.04*
D. bilirubin mg/dL	0.08 ± 0.03	0.15 ± 0.11*	0.22 ± 0.13*	0.08 ± 0.03	0.04*
TWEAK pg/mL	391.7 ± 67.7	635.5 ± 112.7*	945.6 ± 148.9**	385.2 ± 62.9	0.001*

NAA: Not acute appendicitis (normal), Simple AA: Simple appendicitis, Severe AA: Severe appendicitis.
Data are presented as mean ± SD.
(*): Statistically significant difference (p≤ 0.05).

Table 3. Comparison of the markers in acute appendicitis

	n (250)	Sensitivity	Specificity	PPV	NPV

WBC
   Positive (149 TP/53 FP)
   Negative (26 TN/22 FN)
	202
	48
		87.13%	32.91%	73.76%	54.17%

CRP
   Positive (135 TP/73 FP)
   Negative (22 TN/20 FN)
	208
	42
		87.1%	23.16%	64.9%	52.38%

D. bilirubin
   Positive (102 TP/89 FP)
   Negative (52 TN/17 FN)
	191
	69
		85.71%	36.88%	53.4%	75.36%

TWEAK
   Positive (159 TP/29 FP)
   Negative (54 TN/8 FN)
	188
	62
		95.21%	65.06%	84.57%	87.1%

TP: True positive, FN: False negative, FP: False positive, TN: True negative, PPV: Positive predictive value, NPV: Negative predictive value.

Table 4. Comparison of the markers in appendicitis severity						
	n (168)	**Sn**	**Sp**	**PPV**	**NPV**	**Cut-off value**

WBC
  Simple (68 TN/58 FN)
  Severe (25 TP/27 FP)
	116
	52
		30.12%	71.58%	48.08%	53.97%	14.4
						(x10^9/L)

CRP
  Simple (53 TN/59 FN)
  Severe (31 TP/25 FP)
	112
	56
		34.44%	67.95%	55.36%	47.32%	12.9
						(mg/L)

D. bilirubin
  Simple (51 TN/46 FN)
  Severe (32 TP/39 FP)
	97
	71
		41.03%	56.67%	45.07%	52.58%	0.17
						(mg/dL)

TWEAK
  Simple (99 TN/16 FN)
  Severe (48 TP/5 FP)
	115
	53
		75 %	95.19%	90.57%	86.09%	743
						(pg/mL)

TP: True positive, FN: False negative, FP: False positive, TN: True negative, Sn: Sensitivity, Sp: Specificity, PPV: Positive predictive value, NPV: Negative predictive value.						

A correlation between the studied markers and the severity of appendicitis as recorded in operative and pathology reports was also analyzed. Serum TWEAK levels were significantly more sensitive for severity of appendicitis than other markers (Table 4).

DISCUSSION

Acute appendicitis is the most prevalent cause of abdominal pain and the most common reason for emergency abdominal surgery. It is most frequent between the ages of seven and 15 years old, although it can develop at any age, with a lifetime risk of about 7-8 percent (10). Acute appendicitis is classified into two types based on its severity: simple acute appendicitis (simple AA) and severe acute appendicitis (severe AA). Simple AA comprises both simple and suppurative appendicitis (without gangrene, perforation, and abscess formation). Gangrenous appendicitis and other acute appendicitis that can lead to abscesses and perforations are examples of severe AA.

Acute appendicitis is often diagnosed based on a clinical history and physical examination, which are supplemented by subsequent test data such as WBC and differential blood counts. Early and precise diagnosis is critical for effective treatment of acute appendicitis. However, the accurate diagnostic percentage ranges from 72% to 94%. The incidence of negative appendectomy varies between 15% and 34%. These figures demonstrate how difficult it is to make a diagnosis (11).

Standard blood tests such as white blood cell (WBC) count, neutrophil count, C-reactive protein (CRP), bilirubin, alanine transaminase (ALT), and albumin have been used as markers for acute appendicitis, and novel blood markers such as procalcitonin, interleukin-6 (IL-6), serum amyloid-A (SAA), granulocyte colonystimulating factor (G-CSF), and calprotectin (12).

WBC, bilirubin, and CRP are often used indicators for the diagnosis of acute appendicitis, however the severity of acute appendicitis could not be effectively measured due to poor sensitivity and specificity for separating CAA from UAA (13). However, it is critical to categorize the severity of acute appendicitis. There is currently no way for properly predicting severity.

Modern imaging may improve diagnostic accuracy, but its usage may be restricted by availability, cost, and radiation exposure. Difficulties in diagnosing acute appendicitis have led to an ongoing search for new diagnostic indicators that may reduce radiation exposure and expenditures (3).

So yet, no biomarker has been proved to have sufficient diagnostic performance to be employed therapeutically in isolation. This would imply that future research should focus on the development of fresh unique diagnostic tests and their clinical value, rather than repeating earlier research into already examined biomarkers (14).

Kessler et al. reported a 69% elevation in the WBC count of appendicitis patients and a 56% elevation in non-appendicitis patients, with a sensitivity of 77% and a specificity of 63% at a level above 10.000 cells/lL (15). Allister et al. reported that the appendicitis patients had elevated WBC values that were greater than those of the control subjects (14.200 cells/lL vs. 10.600 cells/lL) (16). A meta-analysis by Kabir et al. has demonstrated that a WBC count in isolation is not a good marker to use for diagnosing appendicitis as it can be elevated in response to any inflammatory condition (17). Shogilev et al. describe multiple different cut-off values ranging from 9.4 to 14.6 (x10^9/L) with no clear recommendation on which one is best in the context of identifying acute appendicitis (18). Keohane et al. found that WBC count had the lowest sensitivity (75%) and specificity (63%) of the three blood results they examined (12). The broad range of results is evident in a review by Shogilev et al., which showed that elevated WBC has a sensitivity range between 62% and 87%, and specificity between 39% and 82% (18). Results from our study (sensitivity 87.1%, specificity 32.9%) fall comfortably

within this broad range and are similar to recent metaanalysis by Shogilev et al.

The limited diagnostic accuracy of high WBC is most likely related to the presence of the underlying broad inflammatory process found in acute appendicitis, as well as a variety of other inflammatory disorders (14).

As a result, we think that the WBC count has limited diagnostic usefulness in distinguishing appendicitis in individuals with pain in the right lower quadrant.

When it comes to appendicitis, CRP also plays a varying role in the literature. CRP is an acute phase protein that can be utilized as a marker and diagnostic tool in several inflammatory and disorder-related episodes. A meta-analysis exploring the diagnostic accuracy of CRP revealed a very wide range of sensitivity and specificity (47-74%, and 55-89%, respectively) (19,20). Other studies investigating the role of CRP in diagnosing AA have reported sensitivities ranging between 76.5% and 95.6%, specifities ranging between 26.1% and 77.7%, and PPV 95.6. 2 (19). CRP has a higher sensitivity but a poorer specificity when compared to other measures. In this investigation, CRP levels were within normal limits in several AA patients. This situation may be explained by the fact that CRP levels begin to rise 12-24 hours after the onset of symptoms (19,21). Kabir et al. indicated that CRP is better for detecting complicated or late-stage appendicitis as it is a lag indicator and is less useful for early-stage appendicitis (17). Other papers have also demonstrated that it is less useful for acute appendicitis but significant elevation is suggestive of abscess or perforation (12).

Jasper J. Atema et al. conducted a large multicentre retrospective review of five cohort studies of 1024 adult patients with clinically suspected AA who presented with a duration of symptoms ranging from two h to five days were included (22). They found 12 (11.8%) patients among those with normal IM had a final diagnosis of appendicitis. The conclusion was: No WCC count or CRP level can safely and sufficiently confirm or exclude the suspected diagnosis of acute appendicitis in patients who present with abdominal pain of five days or less in duration (22). Beltran et al. accessed high sensitivity for WBC counts and CRP levels (sensitivity, 0.9-1.0) to differentiate between patients with and without appendicitis, but low specificity (0.2-0.4) was observed (23).

Elevated CRP has shown a similar broad range of results, with sensitivity ranging between 57% and 91% and specificity 26% and 84% (24). The CRP figures for the sensitivity and specificity in our research were 87.1% and 23.1%.

The limited specificity of increased CRP in these data is likely related to the presence of the underlying widespread inflammatory process found with acute appendicitis, as well as a number of other inflammatory diseases. As a result, we feel

the CRP test has limited diagnostic usefulness in the diagnosis of appendicitis.

Although some studies have found hyperbilirubinemia to be effective in diagnosing acute appendicitis, its clinical use remains debatable. Over the last decade, researchers have looked at the link between hyperbilirubinemia and appendicitis. Hyperbilirubinemia occurs in systemic infections caused by a variety of diseases, including general peritonitis and sepsis, and multiple processes underlying hyperbilirubinemia in systemic infection have been identified (25). Bilirubin was reported to have the highest sum of sensitivity (0.61) and specificity (0.61) with a threshold of 15 μmol/L by Kaser et al (26).

On the other hand, Abdelhalim et al. demonstrated that an elevated bilirubin has a specificity of 0.84 and positive predictive value of 0.94 for acute appendicitis, higher than both WBC and CRP. However, its sensitivity was low at only 0.44. When only cases of perforated appendicitis were considered, it was found that the specificity of an elevated bilirubin was only 0.63 and the PPV was 0.20. They argued that these findings contradict prior research that recommended for the use of serum bilirubin to diagnose acute appendicitis with perforation (27). They discovered that serum bilirubin was a poor predictor of these individuals and would not advocate its use in detecting them (27). Also Nevler et al. suggested that elevated serum bilirubin and ALT levels not purely specific for acute appendicitis (3). Results from our study (sensitivity 85.7%, specificity 36.8%) are similar to by Abdelhalim et al (27).

TNF-α was one of the first soluble protein factors to be characterized in the setting of septic illness. Other members of the TNF superfamily have recently been found to have a comparable function to TNF in the pathophysiology of viral or inflammatory disorders (28,29). TWEAK was discovered to cause apoptosis in a human cancer cell line. It has previously attracted attention as a critical regulator of inflammation and cell death in numerous cells and pathological situations, despite having a far greater tissue distribution than TNF. TWEAK occurs as a membrane-bound protein as well as a soluble variety that results from endoproteinase proteolytic cleavage. Both TWEAK-variants are biologically active after attaching to the Fibroblast growth factor-inducible 14, which serves as their genuine receptor. TWEAK serum concentrations have lately been characterized as changing in the setting of several inflammatory and cardiovascular disorders (28).

The current study is the first to look at TWEAK levels in acute appendicitis. TWEAK, WBC, CRP, and direct bilirubin levels were compared. When compared to the other biomarkers evaluated, TWEAK had a high sensitivity and specificity. TWEAK outperformed and outperformed all other markers in all groups. We discovered that serum TWEAK levels were associated to the degree of inflammation in acute appendicitis. With a sensitivity

of 95.2 percent and a specificity of 65 percent, our study completely investigated the diagnostic utility of TWEAK in patients with acute appendicitis, indicating the potential benefit in identifying acute appendicitis. Our results also showed that serum TWEAK was significantly higher in the severe AA group than in the simple AA group. ROC analysis showed that TWEAK had the largest AUC [0.987 (0.965-1.000)] for diagnosis severe AA, having cut-off value 743 pg/mL (sensitivity 75%, specificity 95.2%).

TWEAK concentrations were considerably greater in acute appendicitis patients compared to healthy persons, and plasma TWEAK levels indicated significant differences between severe AA and severe AA, indicating that this TWEAK has predictive value as a severity measure for the first time.

Despite certain limitations, our study had a relatively small cohort for acute appendicitis and illness severity, as well as being a single-center investigation.

There was no published evidence on the role of TWEAK in patients with acute appendicitis prior to the current study. TWEAK may not be a disease-specific marker, but its amplification in any clinical situation, as demonstrated in acute appendicitis in our study, may allow us to anticipate disease severity and hence prognosis. Current and future large-scale population research will aid in determining the utility of TWEAK as an acute appendicitis biomarker and its possible application in clinical practice.

CONCLUSION

In conclusion, increased serum TWEAK levels may be used to aid in the diagnosis of acute appendicitis as well as as prognostic indicators for the severity of appendicitis.

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Akut apandisit şiddetinin belirlenmesinde tümör nekroz faktörü benzeri zayıf apoptoz indükleyicisinin (TWEAK) serum düzeylerinin rolü

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ÖZET

Giriş ve Amaç: En yaygın akut karın nedenlerinden biri akut apandisittir (AA). Pek çok klinik araştırmanın gösterdiği gibi, deneyimli cerrahlar için bile klinik teşhis sıklıkla zordur. Bu çalışmanın amacı, akut apandisit teşhisi için serum TWEAK düzeylerinin kullanılıp kullanılamayacağını görmektir.

Gereç ve Yöntem: Haziran 2017-Mayıs 2019 tarihleri arasında AA tanısıyla ameliyat olan tüm hastalar çalışmaya dahil edildi. TWEAK, WBC, CRP ve bilirubin seviyeleri karşılaştırıldı.

Bulgular: WBC, CRP ve bilirubin seviyeleri patolojiyle karşılaştırıldı. AA hastalarında üç kan göstergesinin tümü önemli ölçüde arttı. Bununla birlikte, basit AA'lı hastalarla şiddetli AA'lı hastalar arasında üç kan göstergesinin düzeylerinde istatistiksel olarak anlamlı bir fark görülmedi. TWEAK plazma konsantrasyonları, şiddetli AA'lı hastalarda sağlıklı kontrol ve NAA gruplarına göre önemli ölçüde daha yüksekti. TWEAK seviyeleri, ciddi AA'lı hastalarda, basit AA'lı hastalara kıyasla anlamlı olarak daha yüksekti.

Sonuç: Yükselen serum TWEAK seviyeleri, akut apandisit tanısının yanı sıra apandisit şiddeti için prognostik gösterge olarak kullanılabilir.

Anahtar Kelimeler: Akut apandisit, enflamasyon, belirteç, apandisit şiddeti, tümör nekroz faktörü benzeri zayıf apoptoz indükleyicisi