RESEARCH ARTICLE

Is ischaemic modified albumin a marker in osteomyelitis patients?

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Abstract

Objective: To compare the levels of ischaemia modified albumin between osteomyelitis patients and healthy controls.

Method: The cross-sectional prospective study was conducted at Van Yüzüncü Yıl University, Van, Turkey, from May 2018 to May 2019, and comprised inpatients diagnosed with osteomyelitis, and healthy controls. Serum IMA concentrations were determined spectrophotometrically at 470nm wavelength. Serum ischaemia modified albumin levels were measured and compared between the patients and the controls. Data was analysed using SPSS 20.

Results: Of the 77 subjects, 37(48%) were patients and 40(52%) were controls. Serum ischaemia modified albumin level in patients was significantly higher than controls ($p<0.05$). There was a significant correlation between ischaemia modified albumin and C-reactive protein levels ($p<0.05$).

Conclusion: Serum ischaemia modified albumin level in patients was significantly higher than controls ($p<0.05$).

Keywords: Osteomiyelitis, Ischaemia-modified albumin, Receiving operation curve, Biomarker, C-reactive protein.

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Introduction

Osteomyelitis is a common disease characterised by infection in the bone or bone marrow. Infection-causing microorganisms can affect the bone or bone marrow through the bloodstream, neighbouring tissue of the source of infection, or by direct transmission.[1] Although there are different approaches in the classification of osteomyelitis, one of the most common classifications is done as acute, chronic, diabetic foot-related and implant-related osteomyelitis.[2]

When the infection invades the soft tissue around the bone, bone damage and destruction of the vascular structure can be observed.[3] Osteomyelitis treatment is difficult and uses strategies such as a combination of antibiotics, surgical resection, and soft-tissue coverage.[2,4] Diagnosis of osteomyelitis requires a multidisciplinary approach, including laboratory tests, imaging and pathology.[5]

Although there is no serum or plasma biomarker with high sensitivity and specificity in the diagnosis of osteomyelitis, traditional markers of inflammation, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are traditionally used.[6] However, no cut-off values for these tests have been determined for osteomyelitis and differential diagnosis. Therefore, the diagnostic value of ESR and CRP for osteomyelitis has not been fully defined.[7] There is a need for a new blood biomarker to be used in the diagnosis of osteomyelitis and monitoring of treatment response.

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Albumin is the most important transporter protein in the bloodstream. As a result of ischaemic damage, the amino acid at the N-terminal end of the albumin is modified and a structure called ischaemia modified albumin (IMA) is formed. IMA has been proposed to be used as a biomarker, especially in ischaemic conditions, and the Food and Drug Administration (FDA) has confirmed that IMA levels can be used to assess the degree of heart ischaemia.[8-10] In addition, IMA is a biomarker for oxidative stresses. Studies have reported elevated IMA levels in acute rheumatic fever,[11] obstructive pulmonary disease,[12] inflammatory bowel disease,[13] Behçet's disease[14] and type 2 diabetes mellitus (T2DM).[15]

The current study was planned to determine whether serum IMA levels are associated with osteomyelitis and whether it has a prognostic value for the diagnosis of chronic osteomyelitis.

Patients and Methods

The cross-sectional prospective study was conducted at Van Yüzüncü Yıl University, Van, Turkey, from May 2018 to May 2019. After approval from the institutional ethics review committee, the sample size was calculated with 95% power and 2.17 effect size. The sample was raised from among inpatients of either gender referred to the Orthopaedic and Traumatology Clinic who were diagnosed as cases of osteomyelitis. Subsequently, a group of healthy controls was also raised. Individuals with chronic diseases, such as diabetes, chronic renal failure, cardiovascular disease, cancer, and those hospitalized due to infection in the preceding 6 months and diagnosed as osteoporosis were excluded from the patient group. Also excluded were individuals with chronic and acute illnesses, those using herbal remedies to either lose weight or seeking some cure,

and those who had a special diet and exercise programme.

After taking informed consent from the subjects, demographic data, including age, gender, socioeconomic status, family history, and duration of disease, was recorded for each subject.

Blood samples were then collected into tubes without anticoagulants. Serum was obtained by centrifugation at 3500g for 15min and stored at -800°C until assayed.

Analysis of albumin and CRP were performed by autoanalyser (Architect C16000 Abbott diagnostic from USA and NFL BN-II from Dade Behring Germany) using the protocol defined by the manufacturer.

Serum IMA levels in both groups were measured as defined in literature.[8] Serum sample 200µL was taken in a glass tube and 50µL cobalt chloride was added. The mixture was incubated for 10min at room temperature. Dithiothreitol 50µL was added to the mixture. After 2min, 1ml sodium chloride solution was added. IMA concentrations were calculated by measuring the absorbance of the coloured complex at 470nm wavelength.

Data was analysed using SPSS 20. Mean±standard deviations (SD) were calculated. Normal distribution of data was checked with Shapiro-Wilks test and equal variance F-test. Independent sample t test was used for comparison of osteomyelitis between the groups. Receiver operating characteristic (ROC) curve was performed. Spearman test was used for correlation analysis. P<0.05 was considered significant.

Results

Of the 77 subjects, 37(48%) were patients and 40(52%) were controls. Among the patients, there were 26(70.3%) females and 11(29.7%) males with an overall mean age of 56±4 years, while there were 25(62.5%) females and 15(37.5%) males with an overall mean age of 58±6 years in the control group (p>0.05) (Table 1).

Table-1: Demographic characteristics.

	Patients with Osteomyelitis (n=37)	Healthy Controls (n=40)
Age (years)	47.9±21.9	42.7±18.1
Gender (male/female; f)	11/26	15/25
Duration of Illness (days)	8.7 (6.4-9.8)	NA
Causative agent (f)		
Staphylococcus aureus	27	
Pseudomonas spp.	3	NA
Streptococcus	2	
Haemophilus influenzae	2	
Others	3	

Albumin level in patient group was significantly lower and CRP level was significantly higher than the control group (p<0.001). Also, osteomyelitis patients showed significant higher IMA level than those of the controls (p<0.001). IMA ratio (IMAr) to albumin was significantly higher the control group (p<0.001) (Figure 1; Table 2).

There was significantly positive correlation between IMA and CRP (r=0.381; p=0.001). However, there was significant negative correlation between IMA and albumin (r=-0.451; p=0.001) (Figure 2).

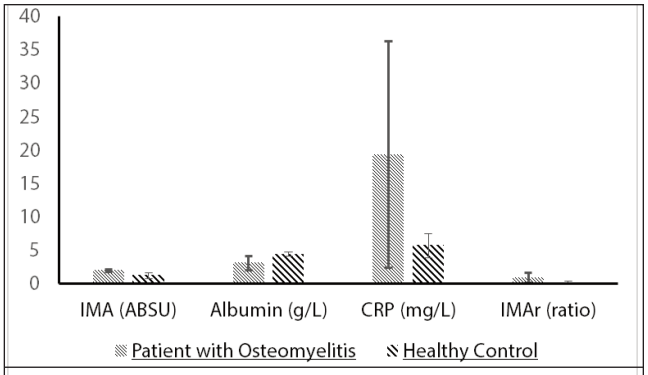

Figure-1: Levels of ischaemia modified albumin (IMA), albumin, C-reactive protein (CRP) and IMA ratio in patient and control groups.

Table-2: Distribution of ischaemia modified albumin (IMA), albumin, C-reactive protein (CRP) and IMA ratio in patients and control groups.

	Patients with osteomyelitis	Healthy control	95 % CI		*p*-value
			Lower	Upper	
Albumin (g/dL)	3.05±1.11	4.37±0.33	-1.71	-0.93	<0.001
CRP (mg/L)	19.3±16.9	5.69±1.81	8.04	19.2	<0.001
IMA (ABSU)	1.95±0.18	1.19±0.46	0.61	0.94	<0.001
IMAr (ratio)	0.86±0.79	0.27±0.11	0.32	0.85	<0.001

CI: Confidence interval. ABSU: Absorbance units

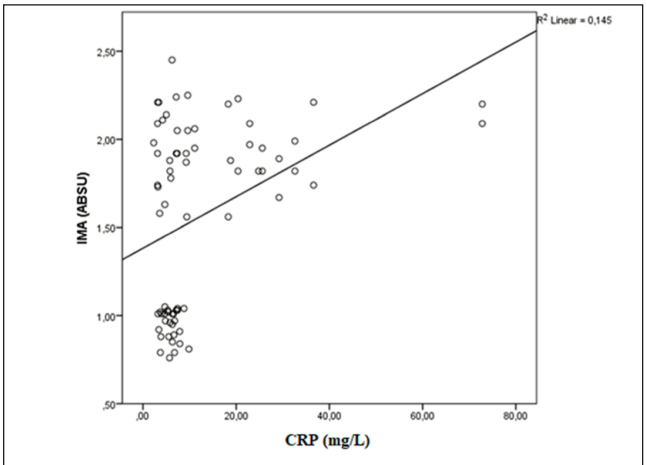

Figure-2: Correlation between ischaemia modified albumin (IMA(and C-reactive protein (CRP): Scatter-dot presentation.

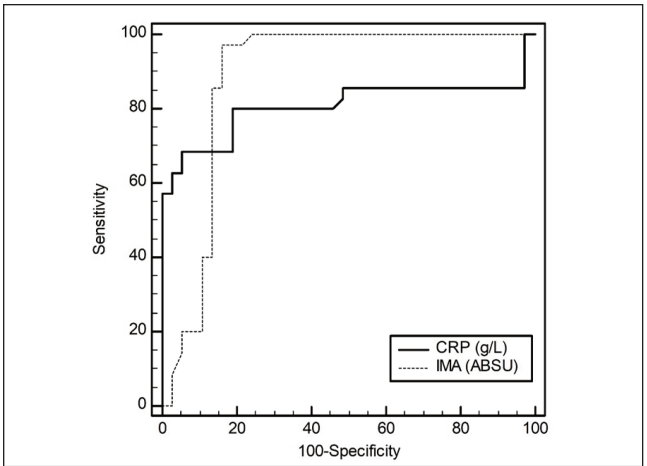

Figure-3: The comparative receiver operating characteristic (ROC) curve of ischaemia modified albumin (IMA) and C-reactive protein (CRP).

Table-3: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of C-reactive protein (CRP) and ischaemia modified albumin (IMA) for predicting osteomyelitis.

Parameters	Overall Volunte00ers			
	Sensitivity (95%CI)	Specificity (95% CI)	PPV	NPV
IMA (ABSU) Cut-off values				
1.63	97.1(85.1-99.9)	83.8 (68.0-93.0)	85 (70.2-94.3)	96.9(83.8-99.9)
1.82	71.4(53.7-85.4)	84.5(71.2-95.5)	83.3 (65.3-94.4)	76.2 (60.5-87.9)
1.99	97.1 (21.5-55.1)	89.2 (74.6-97)	70.5 (50.1-93.3)	60.0 (45.0-73.0)
CRP (mg/L) Cut-off values				
8.8	68.6 (50.7-83.1)	94.6 (81.8-99.3)	92.3 (74.9-99.1)	76.1 (61.2-87.4)
5.01	85.7 (64.7-95.2	40.5 (24.8-57.9)	57.7 (43.2-71.3)	75.0 (50.9-91.3
9.85	57.1 (34.7-73.2)	100 (90.5-100)	100 (83.2-100)	71.2 (56.9-82.9)

ABSU: Absorbance units

The area under the curves (AUC) of IMA was 0.884 (95% CI: 0.773-0.964) and the AUC value of CRP was 0.633 (95% confidence interval[CI]: 0.483-0.766) (Figure 3). There was significant difference between AUC values of IMA and CRP (p=0.0283). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of IMA and CRP for predicting osteomyelitis were also noted (Table 3).

Discussion

Osteomyelitis is a disease caused by bone inflammation, and infectious bone marrow inflammation may occasionally develop. Osteomyelitis can be haematogenous or soft tissue infection. Degraded bone areas defined as sequestrant are protected from immune cells and antibiotics.[3,16] It may also be a complication of surgery or injury caused by microorganisms.[1] Osteomyelitis have an incidence of 21.8 per 100,000 persons / year in the United States.[17]

Radiological imaging is used for the diagnosis of osteomyelitis, and blood tests and microbiology can be used for further confirmation. CRP levels in osteomyelitis are usually high, but may normally be with major pathogens, such as propionibacterium acnes.[18]

The IMA was first identified in the early 1990s and has since been widely studied in patients presenting with myocardial ischaemia.[19] Studies on patients with acute mesenteric ischaemia, heart failure, pulmonary embolism, cardiopulmonary resuscitation, end-stage renal failure (ESRD), cerebrovascular ischaemia, systemic sclerosis, arthroscopic knee surgery, post-exercise skeletal ischaemia and diabetes mellitus have reported increased serum IMA level.[20] Elevated IMA levels were detected in patients with chronic obstructive pulmonary disease (COPD), acute rheumatic fever[12] inflammatory bowel disease[13] and Behçet's disease.[14] In addition, the IMA level also has been found to be increased in prostate, neuroblastoma and sarcomatous children, bladder cancer and colorectal cancer patients.[21-24] There is no study investigating relation between osteomyelitis and serum IMA levels. In the current study, the levels of IMA in patient with osteomyelitis was significantly higher than the controls. Albumin levels in patients with osteomyelitis were significantly lower than those of the controls, indicating that IMA levels were associated with osteomyelitis.

A study reported that the sensitivity of ESR was higher than CRP for osteomyelitis recurrence, and suggested ≥5 mg/L as the cut-off point for CRP (sensitivity: 62.5%; specificity: 58.8%).[25] Another study[25] suggested the cut-off point at ≥14mg/L (sensitivity: 85%; specificity: 83%). The current study found 68.6% sensitivity and 94.6% specificity for ≥8.8 mg/L CRP cut-off point. For IMA, 97.1% sensitivity and 83.8% sensitivity was determined at ≥1.63 cut-off point. In addition, AUC value of IMA and CRP was 0.884 and 0.633 respectively. There was significant difference between AUC values of IMA and CRP (p<0.05).

To the best of our knowledge, this is the first study evaluating the IMA parameter in osteomyelitis. However, the study has its limitations as there was no long-term follow-up and IMA levels were not detected post-treatment.

Conclusion

IMA may have a role in the pathogenesis of osteomyelitis. IMA levels in the serum can be considered as a marker to predict osteomyelitis. IMA level could be used as a guide for osteomyelitis. Also, the IMA level may be predictive of the course of treatment.

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Conflict of Interest: None.

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