Serum ischaemia-modified albumin increases in critical lower limb ischaemia

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ABSTRACT

Background: Ischaemia is a common phenomenon in the pathogenesis of a wide range of medical and surgical conditions, including myocardial infarction, mesenteric vascular occlusion and compartment syndrome. Ischaemia modified albumin has been suggested as an aid to clinical decision making in various clinical settings. This study examines the usefulness of IMA in the diagnosis of limb ischaemia (LI).

Methods: This case-controlled study was performed in the emergency department of Karadeniz Technical University Hospital, Turkey. 22 patients presenting to the emergency departments and definitively diagnosed with LI were enrolled in the study. A control group of 22 healthy volunteers served as a reference for biochemical parameters.

Results: The mean serum IMA level for LI patients was 0.295 (SD 0.062) ABSU. The mean serum IMA level for control patients was 0.174 (SD 0.061) ABSU. There was a statistically significant difference between the mean LI patient and mean control patient IMA levels ($p<0.0005$). A ROC curve analysis reveals the relationship between sensitivity and specificity for IMA in limb ischaemia.

Conclusion: There is a significant increase in serum IMA in limb ischaemia. Furthermore, using a cutoff of 0.22 ABSU, ROC curve analysis shows that IMA is 81.8% sensitive and 81.8% specific 81.8% in patients with clinically severe lower limb ischaemia. Future studies would be needed to determine if IMA would be clinically useful in the diagnosis of subtle limb ischaemia.

Ischaemia is a common phenomenon in the pathogenesis of a wide range of medical and surgical conditions, including myocardial infarction, mesenteric vascular occlusion and compartment syndrome. The diagnosis of such disorders is often clinical, and requires the detection of subtle symptoms and signs essential for timely intervention.[1] Despite years of research, there is no laboratory test for ischaemia that aids clinical diagnosis in these clinically challenging situations. Lactate production from anaerobic metabolism may be measured using a point of care test; other biochemical markers include creatine kinase, myoglobin and the troponins. Their release, however, occurs after significant cellular injury and membrane disruption, so they are usually considered to be markers of necrosis, rather than of ischaemia.[2]

Ischaemia-modified albumin (IMA), however, is regarded as a marker of myocardial ischaemia, in contrast to cardiac enzymes (creatine kinase, creatine kinase–myocardial band and troponins) that are released when cardiac necrosis occurs during cardiac necrosis.[3]

Through hypoxia, acidosis, sodium and calcium pump disruptions and free radical injury, ischaemia may induce changes in the capacity of the amino terminus of the albumin to bind metals such as cobalt, copper and nickel.[1] IMA is a sensitive marker of myocardial ischaemia, skeletal muscle ischaemia, pulmonary embolism, mesenteric ischaemia and stroke.[4–8] The aim of this study was to see whether IMA is a useful adjunct in the diagnosis of lower limb ischaemia. If there is a sensitive and specific relationship between IMA and clinically obvious lower limb ischaemia, a future study might test the usefulness of IMA in the diagnosis of subtle limb ischaemia.

PATIENTS AND METHODS

This case-controlled study was performed in the emergency department of Karadeniz Technical University Hospital, Turkey. The study period was from June 2006 to October 2007.

Twenty-two consecutive patients (mean age 70 years, SD 10) presenting to the emergency department and definitively diagnosed with limb ischaemia using symptoms, signs of physical examination (foot pain, extremity cyanosis, pallor, a cold extremity, no palpable pulse or a combination of these) and hand-held Doppler examination findings (no pulse), were enrolled in the study. The patients were examined by an unblinded emergency physician and blinded vascular surgeon. A definitive diagnosis was make by the vascular surgeon and emergency physician together. Only patients who had had symptoms for 24 h or less were included.

Patients were excluded from the study if they had other ischaemic diseases, such as acute coronary syndrome (ACS), acute myocardial infarction, acute ischaemic cerebrovascular disease, pulmonary embolism or an abnormal serum albumin level. Abnormal serum albumin levels make the determination of IMA levels impossible (normal level 3.5–5.5 mg/dl). Patients were also excluded if they had advanced hepatic, renal or cardiac insufficiency, or troponin-T and electrocardiogram abnormalities suggestive of ACS. Patients under 18 years of age were also excluded and those who refused to participate in the study. In addition, a control group of 22 non-hospitalised consecutive emergency department patients (mean age 65 years, SD 7) served as a reference for biochemical parameters. The exclusion criteria for the control group were the same as for the patient group.

Table 1 Clinical characteristics of patients in the limb ischaemia group (n = 22)

Age (median), years	46–100 (70)
Sex (%)	
Male	13 (59.1)
Female	9 (40.9)
Signs and symptoms	
Pain	22
Cool extremity	22
Pulse loss	22
Cyanosis	12
Numbness	8
Paralysis	4
Co-morbidity	
Atrial fibrillation	12
Diabetes	3
Hypertension	17

Laboratory analysis

Blood samples were drawn on admission. Serum samples were prepared by 15 minutes of centrifugation at 3000 rpm. Specimens to be used for measuring IMA serum concentrations were pipetted into Eppendorf tubes and stored at −80°C.

The reduced cobalt to albumin binding capacity (IMA level) was analyzed using the rapid and colorimetric method of Bar-Or *et al*.[9] The results were reported as absorbance units (ABSU).

Statistical analysis was performed using SPSS for Windows, release 11.0. Each group's IMA levels were tested for normal distribution using the Kolmogorov–Smirnov test. Comparisons between the limb ischaemia group and the control group were performed using Student's t-test. Statistical significance was assumed at a level of $p<0.05$. The area beneath the receiver operating characteristics curve was used to determine the discriminative power of IMA in the diagnosis or exclusion of limb ischaemia.

LIMITATIONS

The inclusion criteria for patients with limb ischaemia in this study are entirely clinical. Although this is somewhat imprecise, the ischaemia in all patients was clinically obvious. Even though the ultimate aim was to find a test useful in mild limb ischaemia, an initial study with unequivocal limb ischaemia is useful. If IMA testing with clinically obvious limb ischaemia is not specific enough at acceptable levels of sensitivity, it is exceedingly unlikely to be useful in more subtle clinical situations.

The inclusion criteria for control patients was also problematical because of the number of pathological and physiological variables that influence serum IMA levels. It was impractical to control for all possible variables.

RESULTS

A total of 44 individuals were investigated, consisting of 22 definitively diagnosed limb ischaemia patients (mean age 70 years, SD 10) meeting the study criteria and 22 healthy volunteers. Four patients were excluded on the basis of predefined criteria: acute ischaemic cerebrovascular disorder (n = 1); advanced kidney insufficiency (n = 1) and advanced heart insufficiency (n = 2).

The general clinical characteristics of the 22 patients in the limb ischaemia group are shown in table 1.

The mean serum IMA level for limb ischaemia patients was 0.295 ABSU (SD 0.062). The mean serum IMA level for control patients was 0.174 ABSU (SD 0.061) (fig 1). There was a statistically significant difference between the mean limb ischaemia patient and mean control patient IMA levels ($p<0.0005$).

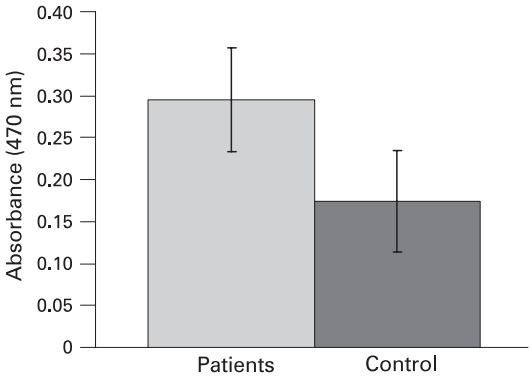

Figure 1 Ischaemia-modified albumin concentrations in patients with limb ischaemia and the control group.

The area under the curve for IMA was 0.91 (bootstrap 95% CI 0.82 to 0.99). The optimum diagnostic cutoff point maximising sensitivity and specificity was 0.220 ABSU, with a sensitivity of 81.8% and a specificity of 81.8% (fig 2). The serum absorbance values of limb ischaemia patients and healthy individuals are shown in fig 3.

DISCUSSION

As a result of initially encouraging results in other types of ischaemia, this study was designed to compare the IMA levels of patients with clinically obvious lower limb ischaemia with control patients. There was a statistically significant difference between the limb ischaemia patients and control patients; receiver operating characteristics curve analysis also revealed that IMA testing even in patients with severe limb ischaemia was at acceptable levels of sensitivity and specificity.

IMA has been proposed as a biological marker of myocardial ischaemia in suspected cases of ACS. Despite the high negative predictive value of a negative IMA in ACS, its cardiospecificity is as yet unproved.[10 11]

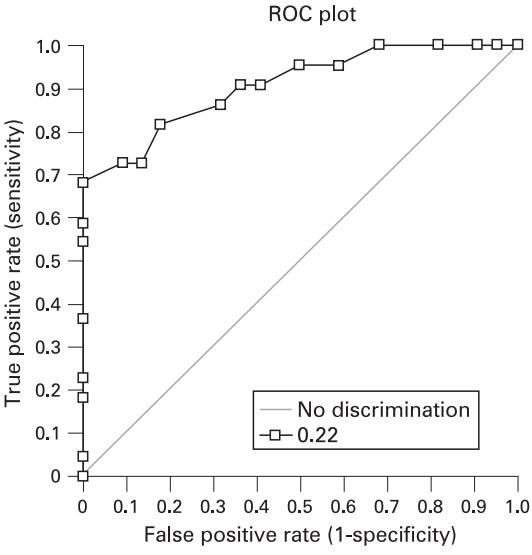

Figure 2 Receiver operating characteristics (ROC) curve.

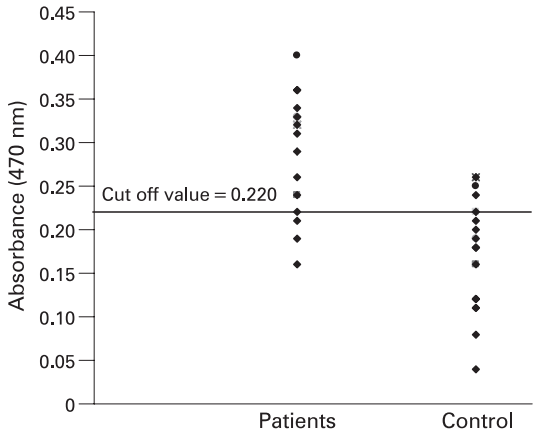

Figure 3 Serum absorbance values of limb ischaemia patients and healthy individuals.

Extracardiac oxidative stress could elevate IMA levels and, therefore, limit the usefulness of elevated IMA levels in the detection of cardiac ischaemia.[11] Gunduz *et al*[7] found elevated IMA levels in mesenteric ischaemia and Turedi *et al*[6] found pulmonary embolism. IMA is also elevated in patients with chronic claudication, aortic cross-clamping and cross-clamping during arterial reconstruction.[2] In a study of marathon runners, Apple *et al*[12] found no immediate change in serum IMA; however, they found an elevation in IMA at 24–48 h. They postulated that there was no acute cardiac or skeletal muscle ischaemia in the immediate postexercise period, but there may have been delayed gastrointestinal or skeletal muscle ischaemia.[12]

A puzzling decrease in postexercise IMA was reported by Roy *et al*[11] when they performed treadmill exercise testing on 22 patients with symptomatic lower extremity peripheral vascular disease. Mean IMA concentrations were significantly lower immediately after maximal, claudication-limited exercise, than at baseline or one hour later.[11]

Zapico-Muniz *et al*[10] proposed an explanation for this apparently paradoxical finding by Roy and colleagues[11]. They suspected that elevated lactate levels interfered with the albumin cobalt binding test for IMA. They confirmed their hypothesis by adding lactate to pooled serum. They found a linear decrease in IMA levels with the addition of lactate.[11] In a recent study, Falkensammer *et al*[13] reported that IMA may represent a clinical marker for skeletal muscle ischaemia, although its lack of specificity requires careful clinical interpretation of data.

Changes in serum albumin concentrations will also affect measured IMA levels. In prolonged exercise, such as marathon running, volume depletion will increase the serum albumin concentration, thus decreasing apparent IMA levels. During operative procedures, intravenous fluid infusion will decrease serum albumin levels, increasing apparent IMA levels.[5 11]

In our own study, there was a significant increase in IMA levels in patients with rest pain and lower limb ischaemia when compared with control patients. IMA is elevated in a number of very different illnesses, including ACS, acute mesenteric ischaemia, pulmonary embolism, skeletal muscle ischaemia and stroke. The measurement of IMA is dependent on a number of external factors. Decreased serum albumin and intravenous fluid administration can lead to apparent elevated IMA levels, whereas elevated lactate and increased serum albumin levels, as in prolonged exercise, yield apparent decreases in IMA levels. In conclusion, IMA levels appear to be elevated in a number of illnesses and are changed by a number of physiological conditions. Despite the previously mentioned confounding variables, serum IMA was 81.8% sensitive and specific in clinically severe lower limb ischaemia. With the significant increase in serum IMA in clinically severe limb ischaemia and acceptable levels of sensitivity and specificity in our study, further studies may show IMA to be a useful adjunct in the diagnosis of more subtle limb ischaemia.

Competing interests: None declared.

Ethics approval: The protocol for the study was approved by the hospital's ethics committee.

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