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Evaluation of the role of serum Ischemia-Modified Albumin as A Marker in Diagnosis of Acute coronary Syndrome in Hemodialysis Patients.

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ABSTRACT

Acute coronary syndrome is a complication in hemodialysis dependent end stage renal disease patients. They have elevated cardiac troponin without cardiac ischemia, which makes diagnosis of acute coronary syndrome challenging. Ischemia Modified Albumin is a new marker used to detect myocardial ischemia. Objective, evaluate the role of Ischemia Modified Albumin as a marker of Acute coronary syndrome on hemodialysis patients. Our study enrolled 60 patients with end stage renal disease on hemodialysis and 30 healthy as control (C). Patients were divided into two groups A (end stage renal disease on hemodialysis with Acute coronary syndrome) and B (end stage renal disease on hemodialysis without Acute coronary syndrome), each one included 30 patients. All groups were subjected to Blood urea nitrogen, cardiac troponin I, and Ischemia Modified Albumin. We found significant increase of cardiac troponin I in A as compared to C, significant increase of troponin I in B when compared to C. Significant increase of Ischemia Modified Albumin in A when compared to C and B, but no significant difference between B when compared to C. Conclusion: we concluded that Ischemia Modified Albumin could help as a marker for myocardial ischemia in end stage renal disease on hemodialysis.

Keywords: Ischemia modified albumin, acute coronary syndrome, cardiovascular complications, ESRD on HD, and chronic renal failure.

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INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem **[1]** and a significant association has been identified between CKD and coronary artery diseases (CAD) **[2]**. CAD increases gradually with the decline of glomerular filtration rates; that means that the end stage renal disease (ESRD) patients have the highest CAD risk among CKD patients **[3].** Furthermore, CKD is proposed as an important risk factor for acute coronary syndrome (ACS) **[2]**.

ACS is a catastrophic clinical event among dialysis patients **[4]** and is responsible for more than 50% of mortality among patients with ESRD **[2]**. The diagnosis of ACS is generally based on the symptoms, ECG findings, and cardiac biomarkers. But the diagnosis of it can be particularly challenging among patients with ESRD because the conventional biomarkers for the diagnosis of myocardial ischemia as troponin I have persistent elevated without clinical evidence of acute ischemia **[5]**.

Ischemia modified albumin is an altered type of serum albumin formed during exposure to ischemic tissues **[6]**. Increased IMA can be detected in the early stages of myocardial ischemia and have been used as a marker for myocardial necrosis **[7]**. Therefore, the aim of this work was to evaluate the role of serum IMA as a marker in the diagnosis of ACS in ESRD on regular HD patients.

PATIENTS AND METHOD

Patients and controls

ESRD on regular HD was the final diagnosis in 60 patients; 36 men and 24 women, their ages ranged between 40 and 60 years. They were divided into two groups (A and B), group A included 30 patients (ESRD／HD) were complaining of typical cardiac chest pain (18 men and 12 women), and group B included 30 patients (ESRD／HD) without chest pain (18 men and 12 women), which selected from hemodialysis units in Al Mokattam Insurance Hospital and Cairo Fatemic Hospital between December 2013 and June 2015. Other 30 apparently healthy persons of matching age and sex were included in the study as healthy control group.

All patients and healthy control before inclusion in the study signed consents and approval of the ethical committee of faculty of medicine, Al-Azhar University was also obtained.
Patients and controls were divided into:

Group A: Included 30 patients had ESRD on regular HD with acute coronary syndrome (28 had ST-EMI - 2 had N-ST-EMT), age ranged between 40 -60 years with mean age of 50.30 ± 7.10.
Group B: Included 30 patients had ESRD on regular HD without chest pain, age ranged between 43 -60 years with mean age of 50.80 ± 5.80.
Group C: Included 30 apparently healthy subjects, 18 females and 12 males with age ranged between 40 -60 years with mean age of 50.80 ± 5.50.

Exclusion criteria:

- Patients with diabetes mellitus.
- Patients with hepatitis C and B viral infection.
- Patients with cerebrovascular stroke.
- Patients with any type of malignancy.
- Patients with acute infections.

All studied participants were subjected to the following:

- Full history taking.
- Full clinical examination was done.
- Laboratory investigations:

  - Serum creatinine (normal: 0.6-1.2 mg/dl).

- Blood urea nitrogen (BUN) (normal: 7-18 mg/dl).
- Serum sodium (normal 135-145 mEq/l.
- Serum potassium (normal: 3.5-5 mEq/l).
- Bilirubin (normal: 0.2-07 mg/dl).
- SGOT (normal: 5-41 IU/l).
- SGPT (normal: 4-37 IU/L).
- Serum Albumin (normal: 3.4-4.7 g/dl).
- Fasting blood glucose (normal: 70-110 mg/dl).
- Cardiac enzymes:

    - Serum CK (normal: 5-35 (males), 5-25 µg/ml (females).
    - Serum CK- MB (normal: 0-3.5 µg/l)
    - Cardiac Troponin I (normal: 0-0.4 mg/ml).
    -

Serum Ischemia modified albumin (IMA): Sampling collection

Five ml of venous blood samples were collected from each subject participating in the study and was left to clot then the serum was separated by centrifugation at 3000 xg for 10 minutes and IMA assay, CK and CK MB and troponin I were performed immediately. The rest of the serum was stored at -20ºC for determination of AST, BUN and creatinine.

Quantitative determinations of:

- The determination of AST, kidney function tests were carried out on Dimension RxL Max analyzer (Siemens Healthcare GmbH - Henkestr. 127, 91052 Erlangen, Germany) by colorimetric techniques.
- The determination of serum CK (using enzymatic method) [8] and serum CK MB (using sandwich enzyme immunoassay) [9] were carried out on Dimension Flex reagent cartridge using Dimension RxL Max analyzer.
- Troponin I was determined on Dimension RxL Max analyzer using sandwich chemiluminescent immunoassay [10].
- Ischemic modified albumin concentration was determined by addition of a known amount of cobalt (II) to a serum sample and measurement of the unbound cobalt (II) by the intensity of colored complex formed after reacting with dithiothreitol (DTT) by colorimeter. An inverse relationship thus exists between the level of albumin bound cobalt and the intensity of the color formed [11].

Statistical Analysis:

The data were collected, revised, coded and entered to the statistical package for social science version 20 (IBM SPSS version 20). The qualitative data were presented as number and percentages while the quantitative data were presented as mean, standard deviations (SD) and ranges.

Comparisons between two groups with qualitative data were done by using Chi-square test while the comparisons between two groups with quantitative data were done by independent t-test.

The confidence interval was set to 95% and the margin of error accepted was set to 5%.

* P-value was considered significant when, P>0.001.
* P-value was considered significant when, P < 0.05.
* P-value was considered significant when, P >0.05.

RESULTS

The results of current study were summarized in the following tables:-

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Table 1 provides the baseline characteristics of the overall study subjects. Acquittal diagnosis of ACS was made in 30 patients had ESRD on HD. Additionally, they had maximum levels of serum AST, serum creatinine, serum Ck, serum CK-MB, cTnI and serum IMA.

Table (1): Baseline characteristics in the overall subjects

parameters	Group A ESRD[a]/HD[b]/ACS[c]	Group B ESRD/HD/No ACS[c]	Group C healthy control
Age / years	50.30 ± 7.10	50.80 ± 5.80	50.80 ± 5.50
Sex (men/women) (n[d])/%	(18/12) (60%/40%)	(18/12) (60%/40%)	(18/12) (60%/40%)
Hypertension	30	30	No
Diabetes mellitus	No	No	No
Cerebrovascular stroke	No	No	No
Heapaitis	No	No	No
Duration of HD[b](rang)/ years	3 to 5 years	2 to 5	No
Chest pain	All of them have typical chest pain	No chest pain	No
Electrocardiogram finding (n[d]. of patients)	28 → have ST-EMI 2 → have NST-EMI	No signs of acute cardiac ischemia.	All subjects have normal finding.
Hypercholesterolemia	30	30	No
Serum AST[e](IU/l)	57.47 ± 15.05	24.97 ± 7.17	20.97 ± 6.45
BUN[f] (mg/dl)	73.33 ± 13.69	73.80 ± 12.44	11.67 ± 3.12
Serum creatinine (mg/dl)	7.22 ± 1.09	7.15 ± 0.98	0.75 ± 0.16
Serum CK[g] (µg/ml)	843.83 ± 409.08	76.33 ± 35.18	63.90 ± 25.55
Serum CK-MB[h] (µg/l)	197.13 ± 87.47	3.93 ± 2.76	2.23 ± 1.04
cTnI[i] (mg/ml)	1.14 ± 0.48	0.06 ± 0.03	0.04 ± 0.03
Serum IMA[j] (U/ml)	96.19 ± 13.98	67.03 ± 8.20	70.10 ± 8.50

a End stage renal disease, b Hemodialysis, c Acute coronary syndrome, d number, e Aspartate aminotransferas, f Blood Urea Nitrogen, g Creatine Kinase, h Creatine Kinase – MB fraction, i cardiac troponin I, j Ischemia modified albumin

Table (2): Comparison between group A (ESRD/HD with ACS) and C (control group).

Parameters	Group (A)		Group (C)		p-value	Sig.
	Mean	± SD	Mean	± SD		
Bun[a](mg/dl)	74.33	13.69	11.67	3.12	<0.001	HS
Serum creatinine (mg/dl).	7.22	1.09	0.75	0.16	<0.001	HS
Serum AST[b](IU/l)	57.47	15.05	20.97	6.45	<0.001	HS
Serum CK[c] (µg/ml)	843.83	409.08	63.90	25.55	<0.001	HS
Serum CK-MB[d] (µg/l)	197.13	87.47	2.23	1.04	<0.001	HS
cTnI[e] (mg/ml)	1.14	0.48	0.04	0.03	<0.001	HS
Serum IMA[f] (U/ml)	96.19	13.98	70.10	8.50	<0.001	HS

a Blood Urea Nitrogen, b Aspartate aminotransferas, c Creatine Kinase, d Creatine Kinase – MB fraction, e cardiac troponin I, f Ischemia modified albumin

The results of the current study had revealed that, there was highly significant elevation of serum BUN, serum creatinine and serum AST in group A patients (who had $ESRD/HD$ with ACS) when compared to group C (control group) (p value < 0.001) (table 2).

Moreover, the current study had revealed that, there was highly significant elevation of BUN in group A patients (who had $ESRD/HD$ with ACS) (74.33± 13.69), when compared to group C (control group) (11.67± 3.12), p value < 0.001. Also the comparison of serum creatinine in group A and (C) was highly significantly increased (7.22 ±1.09) (0.75 ±0.16) respectively, p value < 0.001. And the comparison of serum

AST in group A (57.47±15.05) was highly significantly increased when compared to group C (20.97±6.45), p value < 0.001, as shown in table 2.

When compared between the level of serum CK and serum CK-MB in group A (843.83±409.08), (197.13±87.47), respectively and group C (63.90 ± 25.55), (2.23±1.04), respectively were statistically highly significantly, p <0.001 in both markers. And the comparison of cardiac troponin I {as in table (1)} between group A (1.14± 0.48) and group C (0.04± 0.03) was statistically highly significantly with p value <0.001. Also the comparison of serum IMA in group A (96.19 ±13.98) was highly significantly increased when compared to group C (70.10±8.50), p = (0.001), as shown in table (2).

Table (3) Comparison between group B (ESRD/HD without ACS) and C (control group)

Parameters	Group (B)		Group (C)		p-value	Sig.
	Mean	±SD	Mean	± SD		
Bun[a](mg/dl)	73.80	12.44	11.67	3.12	<0.001	HS
Serum creatinine (mg/dl).	7.15	0.98	0.75	0.16	<0.001	HS
Serum AST[b](IU/l)	24.97	7.17	20.97	6.45	<0.05	S
Serum CK[c] (µg/ml)	76.33	35.18	63.90	25.55	>0.05	NS
Serum CK-MB[d] (µg/l)	3.93	2.76	2.23	1.04	<0.05	S
cTnI[e] (mg/ml)	0.06	0.03	0.04	0.03	<0.05	S
Serum IMA[f] (U/ml)	67.03	8.20	70.10	8.50	>0.05	NS

a Blood Urea Nitrogen, b Aspartate aminotransferas, c Creatine Kinase, d Creatine Kinase – MB fraction, e cardiac troponin I, f Ischemia modified albumin

Table (4): Comparison between group A (ESRD/HD with ACS) and B (ESRD/HD without ACS).

Parameters	Group (A)		Group (B)		P value	Sig.
	Mean	±SD	Mean	±SD		
Bun[a](mg/dl)	74.33	13.69	73.80	12.44	>0.05	NS
Serum creatinine (mg/dl).	7.22	1.09	7.15	0.98	>0.05	NS
Serum AST[b](IU/l)	57.47	15.05	24.97	7.17	<0.001	HS
Serum CK[c] (µg/ml)	843.83	409.08	76.33	35.18	<0.001	HS
Serum CK-MB[d] (µg/l)	197.13	87.47	3.93	2.76	<0.001	HS
cTnI[e] (mg/ml)	1.14	0.48	0.06	0.03	<0.001	HS
Serum IMA[f] (U/ml)	96.19	13.98	67.03	8.20	<0.001	HS

a Blood Urea Nitrogen, b Aspartate aminotransferas, c Creatine Kinase, d Creatine Kinase – MB fraction, e cardiac troponin I, f Ischemia modified albumin

There were highly significant increases in BUN and serum creatinine, in group B (who had without ACS) (73.80±12.44) and (7.15±0.98), respectively, when compared to a healthy group C (11.67±3.12) and (0.75±0.16), respectively, all had the same P < 0.001 (table 2). Also, there were significant increases in serum AST, serum CK-MB and cardiac troponin I (24.97±7.17), (3.93±2.76) and (0.06±0.03) respectively, when compared to control group (20.97±6.45), (2.23±1.04) and (0.04± 0.03) respectively, with P<0.05 for all of them. But when comparing between the levels of serum CK and serum IMA in groups B and C, there were non-significant differences, (P >0.05 in both) (Table 3).

Table (4) showed that, there were highly significant increase as regards serum AST, serum CK, serum CK-MB, cardiac troponin I and serum IMA in group A (57.47 ± 15.05),(843.83 ± 409.08),(197.13 ± 87.47), (1.14 ± 0.48) and (96.19 ± 13.98), respectively, when compared to group B (24.97± 7.17), (76.33± 35.18), (3.93± 2.76), (0.06± 0.03) and (67.03± 8.20), respectively, P <0.001 for all of them. While non-statistically significant difference was found between the two groups as regards to Bun and serum creatinine (74.33 ± 13.69 – 7.22 ± 1.09), respectively and (73.80 ± 12.44 – 7.15 ± 0.98), respectively P value >0.05.

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DISCUSSION

The cardiac biomarkers such as CK-MB and the troponin I which used for the diagnoses of suspected ACS were elevated in ESRD patients on the absence of myonecrosis, thus they have limited role. In 2013, IMA was licensed for diagnostic use in suspected ACS but under search for the diagnoses of suspected ACS in ESRD patients [7]. For that, we evaluate the role of IMA as a marker of ACS in HD patients.

In our study we found that, the cardiac troponin I was highly significant increased in ESRD patients on regular HD with ACS ($P<0.001$), and significantly increased in patients without ACS ($P<0.05$) when compared to healthy subjects. Our result was supported by Jacobs and his colleague, who reported that, the patients with CKD (including those with ESRD) have a greater prevalence of persistently elevated cardiac troponin when compared with subjects who do not have the disease [12]. Meaning that, the cardiac troponin I was elevated in ESRD patients on HD (with or without ACS) that cannot be linked to myocardial injury. Moreover, the value of troponin testing in managing and accessing prognosis in ACS is unclear for this population [5].

Additionally, in current study, the mean serum troponin I showed highly significant increase in ESRD patients on regular HD with ACS when compared to patients without ACS ($P<0.001$). Although, the existence of increased in troponin I in ESRD with ACS patients than in ESRD without ACS and the prognostic implications are less conclusive and overall, troponins have evolved from a marker of “no significance” in ESRD [13]. Also, baseline troponin levels are often not known in patients with CKD on initial presentation, making it hard to define elevated troponin levels [14].

There have been many hypotheses to the cause of serum troponin elevation, may be the result of small areas of clinically silent myocardial necrosis. Pathological evidence exists documenting the presence of such micro-infarctions (small vessel thrombosis) in patients with elevated troponins. These infarctions may be unrecognized clinically and patients with ESRD are more likely to sustain repeated episodes of clinically silent micro-infarctions secondary to their high incidence of CAD. There is also may reflect reduced clearance due to declining residual renal function [15]. Other possible explanation, there is increase of left ventricular mass index and loss membrane integrity which causes troponin I outflow from free cytosolic troponin concentration. There is also a possibility of myocardial cell damage due to uremia contributing to increased serum cardiac troponin I. Beside this Dialysis process itself influences metabolism of cardiac troponin. Most of the HD individuals are predisposed to volume over load and high risk hypertensive events resulting in myocardial stretch [16]. Regardless of mechanism, several observational studies revealed that cardiac troponin I was consistently associated with increased risk of mortality in patients with ESRD [17].

Our study also revealed a highly significant increase in mean serum IMA in ESRD patients on regular HD with ACS when compared to healthy control and ESRD patients on regular HD without ACS ($P<0.001$), but there was no significant difference in ESRD patients on regular HD without ACS when compared to healthy control ($P>0.05$). This means that IMA was raised in cases of myocardial ischemia in ESRD patients on HD. Consistent with our result, the study done by Carrega and his colleagues, 2006, who studied IMA level in cases of HD patients; they found that, there wasn't increase in IMA level in HD patients [18]. And also the study had done by Kiyici and his colleagues 2010, who did not find any difference in IMA levels in either at the beginning or at the end of the dialysis session [19]. Further support for this concept was derived from the study done by Su and his colleagues, 2013, who evaluated the efficiency of IMA for predicting major adverse cardiovascular events in continuous ambulatory peritoneal dialysis patients and showed it highly specific for myocardial ischemia in end-stage renal disease [20].

O ur results were disagreement with Turedi and his colleagues, 2007, who shown that, both pre- and post-dialysis IMA levels are higher in ESRD patients entering HD than in healthy individuals. Anemia is an effect-modifier for the effect of the HD treatment on IMA levels in ESRD patient [21].

CONCLUSION

In our patients, IMA may be useful marker for identification of AMI patients with end-stage renal disease on HD which already had elevated cardiac troponin.

Recommendation: The further research is required to assess the interaction of IMA in CKD with stable angina and ACS in early stage renal disease and ESRD.

Declaration of interest: Local ethics committee approved the study protocol and informed consents were obtained from all subjects.

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