Evaluation of the Complement (C3) in Patients with Acute Coronary Syndrome

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ABSTRACT:

BACKGROUND:

To evaluate complement activation (C3) levels in all forms of acute coronary syndrome (ACS) and to find whether there is any significant changes in C3 concentration at the 1st and 4th day after admission and its relation to clinical outcome.

OBJECTIVE:

Comparing the degree of complement activation (C3 level) between ACS and stable pectoris.To know whether there is any significant difference between the level C3 at first and fourth day. Any correlation between CRP and C3 in patients with ACS.

PATIENT AND METHODS:

129 subjects (94 male and 35 female) age range (41-72 years, mean age 57 ± 10.6) were admitted in this study over the period of Feb 2009-Jan 2010 categorized into three groups; 76 patients with acute coronary syndrome (group A), 25 patients with stable angina (group B) and 28 healthy control (group C). Full clinical, biochemical, electrocardiographic and echocardiographic studies liveredone. All patients were followed to the fourth day of admission, Blood samples from peripheral veins were collected centrifuged and Serum C3 levels were measured using immunokit based on single immunodiffusion.

RESULTS:

The sample of patients was (129) subjects (94 male 72.9%) and (35 female 27.1%). Troponin (I) was positive in 35.7% and negative in 64.3% of the study sample (p. value 0.0005). C-reactive protein (CRP) was significantly correlated with different groups (p. value 0.0004).the same with diabetes mellitus (p. value 0.0003) but not in hypertensive and smokers (p. value 0.486 and 0. 368 respectively).C3levels was significant in correlation to clinical status in both STEMI and NSYEMI 1st and 4th day. Correlation between C3 and C-reactive protein level was insignificant with different groups.

CONCLUSION:

C3 levels was significantly elevated in correlation between ACS compared to patient with stable angina and healthy control subjects. Also C3 level was significant at the fourth day of admission in patients with NSTEMI in correlation to its level at the first day. However no significance associations between C3 levels and CRP in different studied groups.

KEYWORD: acute coronary syndrome, c-reactive protein, C3 level

INTRODUCTION:

There is a growing body of literature suggests a link between systemic inflammation and acute coronary syndromes [1]. Many immunological changes such as basophils, neutrophils, T-lymphocytes, complement activation, IgG and IgE have been implicated in the aetiopathogenesis of myocardial infarction.

The complement system which is composed of >30 serum proteins act as chemotactic stimulatory agents for neutrophils initiate inflammatory process through two pathways (classical and alternative pathways) [2]. These pathways activated by Ag-Ab complexes enhancing the release of mediators such as histamine, leukotriene, prostaglandins with the release of platelets activating factors which produce coronary constriction the final step is lytic stage of myocardial cells and sequential attachment components C3, C6, C7, C8, C9 [3, 4].

Complement factors C3 and C4 are mostly synthesized in the liver and macrophages and also in the infracted heart. C3 and C4 have been used as markers for assessing reperfusion after ischemic episode because complement production indicating complements protein expression in the heart [5, 6, 7, 8].

PATIENTS AND METHOD:

A total of 129 subjects (94 male 72.9% and 35 female 27.1%) (age range 41-72 years, mean age 57 ± 10.6) admitted to Baghdad Teaching Hospital (coronary care unit) over the period Feb 2009-Jun 2010 categorized into three groups.

Group A: 76 patients with ACS (32 female, 44 male) admitted to coronary care unit at Baghdad Teaching Hospital. They were organized into three subgroups.

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Group A1: Thirty one (31) patients (23 male, 8 female mean age 57.419 ± 6.167) with STEMI.
Group A2: Twenty six (26) NSTEMI patients (19 male, 7 female mean age 58.42 ± 7.741).
Group A3: Nineteen (19) unstable angina pectoris patients (14 male, 5 female, mean age 59.421 ± 6.167).
All patients in this study went through usual interrogation of history taking, clinical examination, ECG recoding and biochemical barkers estimation.
All patients with ST elevation myocardial infarction admitted in this study arrived at less than 6 hours of the attack and received thrombolytic therapy.
Group B: Twenty five (25) patients with stable angina (18 male, 7femals, mean age 58.880 ± 5.214).
Group C: control subjects (28) (20 males, 8 female, mean age 55.107 ± 6.355) without history of ischemic heart disease with approximate age distribution, history, physical examination, ECG, chest X ray were all within normal
All patients were followed to the fourth day of admission by clinical examination detecting any abnormal sign and or symptoms plus ECG changes in order to decide whether patient improved or worsened, stationary patients considered improved if he is free of pain, regression of previous ECG changes, stable vital signs.
All patients with personal or family history of asthma, eczema, connective tissue disease evidence of recent infection with high ESR, chronic use of NSAIDs, neoplastic disease, valvular heart diseases, recent (<3 months) major surgery, coronary revascularization have been excluded from the study.
Blood samples were colleced from peripheral veins and sera were separated by centrifugation within 1 hour of collection. These samples taken at the first and fourth day of admission to coronary care unit. Serum C3 levels were quantitatively assayed by using commercially available immunokit (REF-RK00400-LOT-A105.9 from LTA s.r.l. via Milano, Italy).

Statistical analysis:

Values expressed as means ± standard deviation, p. values were expressed for all parameters. Serial C3 levels and their relation to clinical status were compared by ANOVA test. Serial C3 levels and CRP were compared using t-Test for equality of means.

RESULTS:

Table (I) shows the mean difference in C3 levels at the 1st day of admission between all study group (significant) (p. values <0.05). Table (II) illustrates the mean difference in C3 levels at the 4th day of admission between all subgroups of ACS (significant) (p. values <0.05). Table (III) demonstrates the mean of C3 levels at the 1st & 4th day in different clinical situation of different subgroups of ACS and show the significance of C3 levels at the first day of admission especially in worsened group to predicting the clinical outcome.

Table I: ANOVA test shows the relationship between all groups and the mean difference in the C3 levels at the 1st day

(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	(P.V)
STEMI	NSTEMI	12.27283*	4.37585	.006
	UAP	29.57182*	4.79425	.0001
	SA	49.82529*	4.42320	.0003
	Control	62.22915*	4.29002	.0002
NSTEMI	UAP	17.29899*	4.96633	.001
	SA	37.55256*	4.60916	.0005
	Control	49.95632*	4.48151	.0002
UAP	SA	20.25347*	5.00809	.0001
	Control	32.65733*	4.89087	.0004
SA	Control	12.40386*	4.52774	.007

Table II: ANOVA test shows the relationship between all subgroups of ACS and the mean of C3 levels in the 4th day which is significant as P. value is <0.05

(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	(P.V)
STEMI	NSTEMI	9.94107	4.24061	.022
	UAP	30.31698	4.64607	.0003
NSTEMI	UAP	20.37591	4.81284	.0001

Table III: Shows mean of C3 levels at the 1st & 4th day in different clinical situations of different subgroups of ACS.

Group	Status		C3 Level	
			First day	Fourth day
STEMI	Improved	Mean	159.3833	161.5667
		N	12	12
		Std. Deviation	18.55610	14.01852
	Worsened	Mean	170.4600	188.3400
		N	5	5
		Std. Deviation	13.68020	10.97374
	Stationary	Mean	163.1286	174.6786
		N	14	14
		Std. Deviation	14.90490	17.69351
NSTEMI	Improved	Mean	148.2500	152.3583
		N	12	12
		Std. Deviation	13.93469	7.96338
	Worsened	Mean	153.7500	174.2375
		N	8	8
		Std. Deviation	9.52080	12.57911
	Stationary	Mean	151.0500	164.3833
		N	6	6
		Std. Deviation	16.74476	15.18860
UAP	Improved	Mean	129.6182	133.8273
		N	11	11
		Std. Deviation	16.25785	12.04252
	Worsened	Mean	139.3000	133.1000
		N	1	1
		Std. Deviation	.	.
	Stationary	Mean	138.2000	151.8714
		N	7	7
		Std. Deviation	11.91959	11.67458

Table (IV) demonstrates the percent of change between 1st and 4th day in C3 levels in ACS and its relationship to the clinical status where it was a significant in ST elevation myocardial infarction & non ST elevation myocardial infarction (P. values 0.019 & 0.002 respectively) it was non-significant in unstable angina (p. values 0.182). Table (V) confirms that there is non-significant relationship between C3 levels and CRP positivity in all study group (p. values >0.05).

Table IV: ANOVA test shows the mean of the percent of change between 1st and 4th day in C3 levels in ACS & its relationship to the clinical status.

Groups	Status	No.	Mean	SD	P. value
STEMI	Improved	12	0.0218	.11213	0.019
	Worsened	5	0.1788	.09504	
	Stationary	14	0.1155	.10587	
	Total	31	0.0895	.11894	
NSTEMI	Improved	12	0.0411	.08853	0.002
	Worsened	8	0.2049	.08845	
	Stationary	6	0.1333	.08133	
	Total	26	0.1128	.11066	
UAP	Improved	11	0.0421	.11014	0.182
	Worsened	1	0.1380	.	
	Stationary	7	0.1367	.09352	
	Total	19	0.0820	.10939	

Table V: The relation of C3 levels to CRP in different study groups

Groups	CRP	N	C3 level		P. value
			Mean	.SD	
STEMI	+ve	24	161.654	16.017	0.451
	-ve	7	167.0002	17.338	
NSTEMI	+ve	20	150.740	14.081	0.917
	-ve	6	150.083	10.488	
UAP	+ve	15	133.413	15.456	0.945
	-ve	4	132.825	12.950	
SAP	+ve	11	115.970	23.719	0.622
	-ve	14	110.728	27.661	

DISCUSSION:

This study showed that complement component C3 was elevated in almost all patients with ACS in the first twenty four hours and the elevations were significantly more pronounced in the fourth day. Thereafter in our study there was C3 increment even in patient with stable angina pectoris to a lesser extent within the normal range (91-156mg/dl) [9, 10].

Also it was found that a significant elevation in C3 level in patients with (STEMI and NSTEMI) and this fit with some international studies [11, 12].but still does not fit with other studies in which there was no significant complement changes in the plasma of patient with acute myocardial infarction [13, 14] and this difference in the result probably related to the severity of clinical situation in patients with ACS because C3 component might be produced by infarction cardiomyocytes [15, 16, 17].

Myocardial cell necrosis result in the release of subcellular membrane constituents rich in mitochondria which are capable of triggering the early acting components (C1, C2, C3, C4) of the complement cascade [18].

Also this study showed that the level of C3 at 4th day and percent change of its levels to the 1st day is significant in both STEMI and NSTEMI highly significant in NSTEMI subgroup (p. value 0.002) while it is non-significant in unstable angina pectoris subgroup (p. value 0.180) [17, 19, 20].

The level of C3 at the first day of admission might predict suggestion about worsening or improving of patients of STEMI or NSTEMT i. e. improved STEMI patients was (159.383 ± 18.556) while in the worsened patients in the same group was (170.46 ± 13.68). Also the same finding was seen in NSTEMI patient group (improved 148.25 ± 13.93) (worsened 153.75 ± 9.52). Complement activation might lead to myocardial injury through the formation of (membrane attack complex) and the generation of anaphylatoxins [21, 22].Complement activation could be initiated by infusion of thrombolytic agents but in

our patients we used recombinant tissue type plasminogen activator (rTPA) which does not activate C3 and the terminal component from C5 through C9. So C3 level will not be affected in our group of patients [23].

This study showed no significant association between the complement C3 & CRP.

CRP may activate complement system by binding to modified LDL with exposed phosphorylcholine [24] at the deep intima area of atherosclerotic coronary artery lesion. The reason for insignificant correlation between CRP level and C3 component complement might be related to the locally elevated C3 component at the necrosed myocardium and its measurement at the peripheral blood [25, 26, 27]. Also local release of IL-6 might give feedback order to the liver to produce more CRP making the correlation between CRP & C3 component insignificant.

CONCLUSION:

1-C3 levels were significantly elevated in patients with ACS compared with stable angina and healthy control subjects.

2-C3 levels at the forth day might predict clinical outcome.

3-No significant correlation between the complement C3 levels and CRP positivity in different study groups.

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