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Study The Role of Co-Peptin versus Vascular Cellular Adhesion Molecules (VCAM-1) in Cirrhotic Patients with Hepatorenal Syndrome - Acute Kidney Injury

Mohammed A. Omar Abo-Zeid [1,*] M.B.B.Ch., Mohammed E. Kobeisy [1] MD., Haitham A. Abd El-Rahman [1] MD. and Mohammed M. Abo-El fottoh [2] MD.

** Corresponding Author:*
Mohammed A. Omar Abo-Zeid
mohamedabood74@yahoo.com

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[1]Department of Internal Medicine, Faculty of Medicine, Al-Azhar University, Assiut, Egypt.

[2]Department of Biochemistry, Faculty of Medicine, Al-Azhar University, Assiut, Egypt.

ABSTRACT

Background: Advanced cirrhosis is a state marked by synthetic and vascular decompensation, rise in splanchnic blood volume, hyper-dynamic condition with, systemic vasodilatation, AKI is one of the side-effects of cirrhosis, happening in about 45% of hospital stayed cases, and was accompanying with higher death.

Aim of the work: To compare between co-peptin versus VCAM-1 as a biomarker for early detection of HRS-AKI in decompensated cirrhotic patients.

Patients and Methods: This study was conducted between January 2020 and June 2021, on 80 patients attending to Al-Azhar University Assuit branch, Egypt during the time of the study. This work included three groups: Control Group (I): (15 Patients) age and sex-matching controls, Group (II): 40 cases with liver cirrhosis without AKI and Group (III): 40 liver cirrhosis patients with AKI. The study included patient 40 cases with liver cirrhosis without AKI and 40 liver cirrhosis patients with AKI.

Result: A high significantly positive association among VCAM -1 and Co-peptin in group (A) was observed (Pvalue<0.001), additionally, there was a significantly positive correlation among VCAM -1 and co-peptin in group (B),(P=0.027), lastly, there non-significant correlation between VCAM -1 and co-peptin in group C (p=0.315)

Conclusion: Cases with de-compensated liver cirrhosis and HRS-AKI have marked increase in co-peptin, VCAM-1in comparison with cases with decompensated cirrhosis with no HRS.

Keywords: *Acute kidney injury; Co-peptin; cirrhosis; Hepatornal syndrome; Vascular Cellular Adhesion Molecule – 1.*

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INTRODUCTION

Hepatorenal syndrome (HRS) is a defined as kind of hepatorenal diseases (HRD) with a different pathophysiology.[1] HRS is marked by splanchnic arterial vasodilatations and reduced effective intra-vascular volume that resulting in renal vasoconstrictions and reduced renal blood flowing.[2] The Acute Dialysis Quality Initiative (ADQI) in 2012 defines AKI as 2 sub-types of HRS were defined.[3]

Serum Creatinine tends to over-estimate renal functions in patient with cirrhosis, because of reduction in hepatic synthesis of creatinine, malnutrition and volume over load.[4] Co-peptin result from breakdown of arginine vasopressin (AVP), which synthesized in hypothalamus and stores in posterior pituitary. co-peptin has been involved in many diseases as congestive heart failure, chronic obstructive airway diseases.[5] Recently liver cirrhosis pathogenesis can be explained as systemic inflammatory state, which gradually progresses from compensated to decompensated state.[6] Recent studies give a new concept about HRS mechanism. marked systemic inflammatory condition which accompanying with raise level of some inflammation markers as IL 6, ICAM1 and, VCAM1. Vascular Cellular Adhesion Molecules (VCAM-1) , is an inflammatory intermediary that has a principal function in activating the procedure of systemic inflammations.[7]

The study aimed to compare between co-peptin versus VCAM-1 as a biomarker for early detection of Hepatorenal syndrome-Acute Kidney Injury in decompensated cirrhotic patients.

PATIENTS AND METHODS

This study was conducted between January 2020 and June 2021, on 80 patients attending to Al-Azhar

University Assuit branch, Egypt during the time of the study. This work included three groups: Control Group (I): (15 Patients) age and sex-matching controls, Group (II): 40 cases with liver cirrhosis without AKI and Group (III): 40 liver cirrhosis patients with AKI. The study included patient 40 cases with liver cirrhosis without AKI and 40 liver cirrhosis patients with AKI diagnosis was based on combination of the following: clinical data such as All cases were submitted to full history taking including age, sex, cause of cirrhosis (hepatitis C, hepatitis B and other). Complication history connected to cirrhosis (ascites, hepatic encephalopathy, portal HPT or connected bleeding). DM and HPT history thorough general clinical examination, including different body systems. Abdominal and pelvic ultrasound performed to confirm the diagnosis of liver cirrhosis, detection of ascites and portal hypertension. Laboratory investigations as liver and kidney function tests, complete blood counts, serology markers and PCR for positive cases. Measurement of S. vascular cell adhesion molecule-1(VCAM-1)[21] and co-peptin by ELISA technique. Exclusion criteria was included patients with chronic kidney disease without liver cirrhosis or managed with hemodialysis previous to enrollment, cases with preceding liver or kidneys transplantations or on chemo-therapy, cases with hepato-cellular carcinomas beyond Milan criteria, cases with progressive chronic respirational or heart diseases, cases with severe extra-hepatic disorders with poor short-term pronging and lack of informed consent or refuse to be registered in our work.

Statistical analysis has been performed using IBM-SPSS-24 (IBM-Cor, USA). Data have been presented as (mean ± SD), numbers and percentages. Means and SD were utilized for quantitative data. Student t testing has been utilized for comparison between 2 groups, and one-way analysis of variances (ANOVA) testing has been utilized for comparison between more than 2 groups. Mann-Whitney and Kruskal-Wallis test has been utilized as an alternative of student t testing and ANOVA for non-parametric data for comparison between medians rather than means among 2 or more groups; resp. Uni-variable and multi-variable regression made to determine HRS AKI risk-factors. Pearson Chi square testing has been utilized for comparison between percentages of qualitative data, and Fisher's exact testing has been utilized instead for non-parametric data. Pearson correlation testing has been utilized for comparison of 2 quantitative variables. Results were Non significant at P value>0.05, Significant at P value< 0.05 and Highly significant P value < 0.001.

RESULTS

Ninety-five patient were enrolled in this work allocated to 3 groups: Group (I) 15 healthy patients as a control, Group (II) was comprised (40) cases had liver cirrhosis without HRS and Group (III) was comprised (40) cases had liver cirrhosis with HRS.

A non-significant change was found among the studied groups regarding age (p=0.097), female predominance observed in all groups with non-significant variance (P value=0.128) (Table 1). HCV is the mutual reason of cirrhosis in cases' groups with significant difference (p=0.006) (Table 2 and Figure 1). A highly significant change was found among the studied groups A and B as regards complications of cirrhosis (p<0.001) (Figure 2). There was high significant difference between the study groups as regard laboratory investigations (p<0.001) except for ALT and WBCs (p = 0.645, 0.621 respectively) (Table 4). A highly significant change was found among the studied groups A&B as regards CTP (P value<0.001). Mean of VCAM-1 was high in group (B) in comparison to other groups (9.95±7.6, 8.7±5.8, 4.04±1.71 resp.) with highly significant change (p value<0.001). Also, mean of Co-peptin was higher in group B in comparison with other groups (2.09±3.1, 1.78±1.6, 1.7±1.38 resp.) with significant change (p value=0.003). Association among VCAM -1 and Co-peptin levels in this study showed that, there was a highly positive and significant association among VCAM -1 and Co-peptin in group A (P<0.001), additionally, there was positive and significant correlation between VCAM -1 and Co-peptin in group B (P=0.027), however a non-significant correlation was found between VCAM -1 and Co-peptin in group C (p=0.315) (Table 3 and Figure 3).

Variables		AKI-HRS (n=33)	Controls (n=38)	P. value
Age		63.17± 8.39	63.74 ± 6.162	0.75
Sex	Male	27 (81.1%)	26 (68.4%)	0.2
	Female	6 (18.2%)	12 (31.6%)	
Infection on admission	No	16(57.1 %)	17(60.7%)	0.77
	Yes	12(42.9 %)	11(39.3%)	
Mean arterial blood pressure		84.2±13. 7	88.9± 9	0.252
Cause of Cirrhosis	HCV	22 (88%)	32 (90%)	0.12
	HBV	1 (4%)	0 (0%)	
	Cryptogenic	2 (8%)	0 (0%)	
	Cardiac	0 (0%)	2 (6.1%)	
	Budd Chiari	0 (0%)	1 (3%)	
Comorbidities	HTN	3 (15%)	3 (25%)	0.006*
	DM	2 (10%)	7 (58.14%)	
	HTN&DM	7 (35%)	2 (16.7%)	
	NAD	8 (40%)	0 (0%)	

Table 1: Socio-demographic characteristics and clinical history Comparison among the studied groups

* t-test testing has been utilized
**Chi-square testing has been utilized

Variables	AKI-HRS (n=33)	Controls (n=38)	P-value
CRT (0.5-1.2) g/dL	2.5 ±0.90	0.87 ± 0.2	0.000*
AST <34	138.5 ± 18.9	56.5 ± 34	0.000*
ALT (10-49) U/L	62 ± 87.6	36.3 ± 20.2	0.002*
Alb (3.4-5.4) g/Dl	2.0 ± 0.6	2.5 ± 0.6	0.2
T. bil. (5-21) 1.1ol/L (mg/dl)	99.1 ± 13.71	28.02 ± 19.19	0.000*
INR (0.8-1.1)	1.6 ± 0.44	1.4 ± 0.28	0.08*
VCAM-1	8.7 ± 5.9	10 ± 8.2	0.2
WBCs (4-11) *10^3	9.4± 5.5	7.3 ±3.52	0.02*
Neutrophils (40-75) %	72.78 ±10.1	66.4 ±11.9	0.7
lymphocytes (20-45) %	14.2 ±6.2	21.5 ±8.7	0.01*
N/L ratio	6.1 ±2.9	4.0 ±3.03	0.3
MELD-Na	24.6 ±6.6	15.1 ±4.3	0.02*

*Statistically significant at <0.05

Table 2: Comparison of laboratory investigations among the studied groups

Abbreviations: CRT: creatinine, AST: aspartate aminotransferase, ALT: alanine aminotransferase, Alb: Albumin, T.bil: total Bilirubin, INR: international normalized ratio. VACM-1: vascular cellular adhesion molecule-1, WBCs: white blood cells, N/L ratio: Neutrophils / Lymphocytes ratio, MELD-Na: Model End stage Liver disease-sodium.
*: Independent t-test test was used to compare the mean difference between groups

*: Significant results

*: t-test testing has been utilized

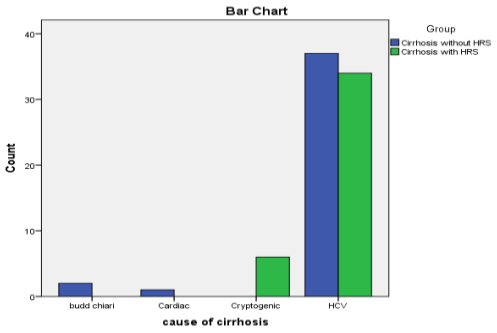

Fig. 1: Bar chart showing the etiology of liver cirrhosis

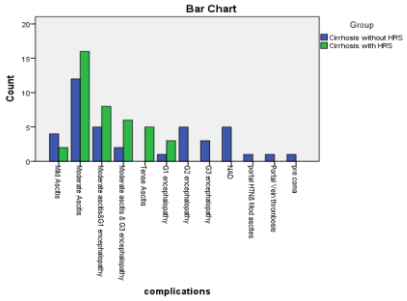

Fig. 2: Bare chart showing the complications of liver cirrhosis.

Variables		AKI-HRS	Controls	P. Value
CTP score		10.01±1.8	8.44±1.5	0.275
CTP class	A	1(3%)	2(5.3)	0.001*
	B	10 (30.3%)	27(71.1%)	
	C	22(66.7%)	9(23.7%)	

Table 3: Comparison of Child Pugh score (CTP) among studied groups.

- t-test testing has been utilized
*Statistically significant at <.05
- Chi-square testing has been utilized

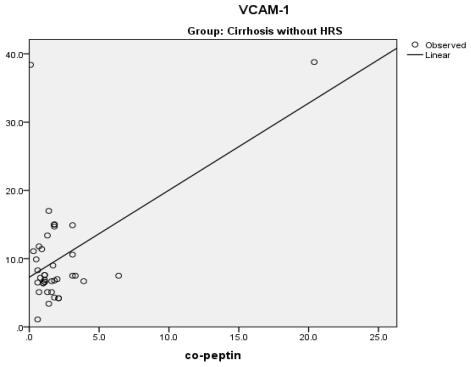

Fig 3: Correlation between VCAM -1 and Co-peptin in group (II)

DISCUSSION

Vascular Cellular Adhesion Molecule -1, (VCAM1) and Co-peptin are inflammatory mediators involved in the procedure of systemic inflammations in responding to numerous stimulations.[7]
The systemic inflammation responding in HRS-AKI cannot explain only by existence of bacterial infection, or kidneys dysfunction severity and isn't regularized by progress of kidneys functions with pharmacological therapy,[8] the severity of the inflammation responding is associated with some inflammation markers, mainly VCAM1, are related with absence of resolutions of AKI.[9] The findings of the present work showed that cases with liver cirrhosis and HRS have noticeable systemic inflammations with changed cytokine profile in comparison with that of cases with de-compensated cirrhosis with no HRS as mean of VCAM-1 and co-peptin were higher in group B in comparison with other groups with highly significant change. This was similar to results obtained by Solé et al.[10] as the findings of their work obviously reveal that as de-compensated cirrhosis advance to HRS-AKI, there is progressive rise in inflammation grade with significant rise in levels of some inflammation cytokines. previous reports revealed that serum levels of inflammation cytokines are elevated significantly in de-compensated in comparison with compensated cirrhosis, which give an important role in the disease progression,[11] but still not clear to be reason or complication of progressions of liver diseases.[12]
Our results settle that this inflammation conditions across de-compensated cirrhosis increases even more

as the diseases developments to HRS-AKI which is measured one of the newest phases of cirrhosis, result in high death rates. this give support to recent studies suggested that systemic inflammation can lead to most of the side-effects of cirrhosis Additional provision to this theory originates from the similarity in between systemic inflammatory response in cirrhosis and that present in some chronic auto inflammation disorders, like inflammation bowel disease some collagen disorders as systemic lupus erythematous or RA (rheumatoid arthritis).[13] the correlation between VCAM -1 and Co-peptin in our study groups, found that positive and high significant association among VCAM -1 and Co-peptin in decompensated in comparison with compensated cirrhosis however there was non-significant correlation in control group. On the other hand, Lefere et al., [14] revealed that S.VCAM-1 expected the existence of significant fibrosis, non-dependent from clinical and bio-chemical cases features. A new report by Yoshimura et al., give idea about the biological events that occur in Japanese cohort study , which recognized VCAM-1 as a hopeful bio-marker to identify the latest stages of hepatic cirrhosis.[15] Previously found that VCAM-1 can give good idea about the prognosis of hepato-pulmonary condition in cases with liver cirrhosis.[16] On the other hand, new trials have as well revealed a strong association among co-peptin and the grade of liver diseases,[17] As report performed by Tawfik et al., [18] found that co-peptin was significantly elevated in decompensated in comparison with compensated cirrhosis group. This is in agreement with Morgenthaler et al., [19] as they revealed that copeptin level raised with more deterioration of liver function, and this biological marker may thus have a prognostic functions. Similar study by Kimer et al, [20] who found that co-peptin level significantly lower with Child A cirrhosis compared with Child C.

CONCLUSION

Cases with de-compensated liver cirrhosis and HRS-AKI have marked increase in co-peptin and VCAM-1 levels in comparison with patients with decompensated cirrhosis without HRS. Our study limited diagnosed patient with cirrhosis AKI based on laboratory and clinical findings which lead to excluding patients with early disease.

Conflict of interest : none

REFERENCES

1. Tandon P, James MT, Abraldes JG, et al. Relevance of new definitions to incidence and prognosis of acute kidney injury in hospitalized patients with cirrhosis: a retrospective population-based cohort study 2016; 11(8):e0160394.
2. Rice JB, White AG, Galebach P, et al. The burden of hepatorenal syndrome among commercially insured and Medicare patients in the United States 2017; 33(8):1473-80.
3. Christ-Crain M, Fenske K. Copeptin in the diagnosis of vasopressin-dependent disorders of fluid homeostasis 2016; 12(3):168-76
4. Francoz C, Durand F, Kahn JA, Genyk. Hepatorenal syndrome 2019; 14(5):774-81.
5. Holwerda D. A Glycopeptide from the Posterior Lobe of Pig Pituitaries: 1. Isolation and Characterization 1972; 28(3):334-9.
6. Solé C, Solà E, Morales-Ruiz M, Fernàndez G, Huelin P, Graupera I. Characterization of inflammatory response in acute-on-chronic liver failure and relationship with prognosis 2016; 6(1):1-10.
7. Vestweber D. How leukocytes cross the vascular endothelium 2015; 15(11):692-704.
8. Hepatol E. (2018) Clinical Practice Guidelines for the management of patients with decompensated cirrhosis 2018; 69(2):406-60.
9. Ginès P, Solà E, Angeli P, Wong F, Nadim MK Kamath P. Hepatorenal syndrome 2018; 4(1):1-17.
10. Solé C, Solà E, Huelin P, Carol M, Moreira R, Cereijo U. Characterization of inflammatory response in hepatorenal syndrome: Relationship with kidney outcome and survival 2019; 39(7):1246-55.
11. Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance 2014; 61(6):1385-96.
12. Girón-González JA, Martínez-Sierra C, Rodriguez-Ramos C, Macías MA, Rendón P, Díaz F. Implication of inflammation-related cytokines in the natural history of liver cirrhosis 2004; 24(5):437-45.
13. Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis 2015; 63(5):1272-84.
14. Lefere S, Van de Velde F, Devisscher L, Bekaert M, Raevens S, Verhelst X. Serum vascular cell adhesion molecule-1 predicts significant liver fibrosis in non-alcoholic fatty liver disease 2017; 41(8):1207-13.
15. Yoshimura K, Okanoue T, Ebise H, Iwasaki T, Mizuno M, Shima T. Identification of novel noninvasive markers for diagnosing nonalcoholic steatohepatitis and related fibrosis by data mining 2016; 63(2):462-73.
16. Raevens S, Coulon S, Van Steenkiste C, Colman R, Verhelst X, Van Vlierberghe H. Role of angiogenic factors/cell adhesion markers in serum of cirrhotic patients with hepatopulmonary syndrome 2015; 35(5):1499-507.
17. Moreno JP, Grandclement E, Monnet E, Clerc B, Agin A, Cervoni JP. Plasma Co-peptin, a possible prognostic marker in cirrhosis 2013; 33(6):843-51.
18. Tawfik AK, Helmy A, Yousef M, Abou-Saif S, Kobtan A, Asaad E. Copeptin as a novel marker predicting prognosis of liver cirrhosis and its major complications 2018; 10:87.
19. Morgenthaler NG, Struck J, Jochberger S, Dünser M. Co-peptin: clinical use of a new biomarker 2008; 19(2):43-9.
20. Kimer N, Goetze JP, Bendtsen F, Moller S. New vasoactive peptides in cirrhosis: organ extraction and relation to the vasodilatory state. European journal of clinical investigation 2014; 44(5):441-52.
21. Rostampou N, Fekri, K, Hashemi-Dehkordi E, Obodiat M. Association between Vascular Endothelial Markers and Carotid Intima-Media Thickness in Children and Adolescents with Type 1 Diabetes Mellitus. Journal of clinical and diagnostic research. 2017;11(9):1-5.