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Serum Levels of Intercellular Adhesion Molecule-1, N-Terminal pro-Brain Natriuretic Peptide and Cardic Troponin-I among Haemodialysis Patients with Hepatitis C Virus

Huda Saad Salman[1], Basim Mohammad Ibrahim[2] and Ahmed Fadhel Al-Khafagi[3]

[1]M.Sc. Student,University of Baghdad,Collage of Medicine, Department of Microbiology; [2]Department of Microbiology, Collage of Medicine, University of Baghdad; [3]Iraqi center of Haemodialysis, Baghdad Teaching Hospital

Corresponding author E-mail:Hoda.Saad1200a@comed.uobaghdad.edu.iq

Abstract

Background: Chronic hepatitis C virus infection is a global health burden that has been associated with many diseases, including coronary artery disease.

Objectives: Determine the risk of coronary artery disease among haemodialysis patients through the measuring endothelial and cardiac biomarkers in their serum.

Methodology: Measurement the levels of intercellular adhesion molecule-1 (endothelial function biomarker), N-terminal pro-brain natriuretic peptide and cardic troponin-I(cardiac dysfunction biomarkers) in the serum of 45 Iraqi patients on haemodialysis infected with hepatitis C virus (patients group), as well as their control group (45 Iraqi patients on hemodialysiswithout hepatitis C virus infection) by the using of Enzyme linked immunosorbent assay technique.

Results: Elevated serum levels of all the above mentioned biomarkers were seen in the patients group in comparison to the control group. Strong positive correlations were found between intercellular adhesion molecule-1 biomarker with bothcardiac dysfunction biomarkers (cardictroponin-I and the N-terminal pro-brain natriureticpeptide)among the patients group. Another positive correlation was revealed between the cardiac dysfunction biomarkers themselves among the patients group.

Conclusions: Patients with hepatitis C virus infection have an increased risk of cardiovascular diseases. The findings of this study indicate the importance of regular screening of such important biomarkers among patients with haemodialysis in order to prevent the risk of such complications.

Keywords:HCV related biomarkers, Endothelial and cardiac biomarkers, Haemodialysis complications.

Introduction

Hepatitis C virus (HCV) infection is an infectious disease affects the liver, leading to cirrhosis and hepatocellular carcinoma (HCC)[1].In Iraq, the prevalence of HCV infection ranged 3.21-7.1% among the general population [2].This virus is transmitted from person to person in many ways; mostly blood and blood products through sharing contaminated needles, diagnostic and therapeutic procedures including dental procedures and haemodialysis (HD) [3].Haemodialysis is a therapeutic procedure described for patients with chronic kidney disease (CKD) for regulating blood pressure and filtering blood from medications and waste products of metabolism[4].Chronic HCV infection and CKD were demonstrated to be associated with subclinical and clinical cardiovascular diseases (CVDs), such as myocardial infarction (MI), congestive heart failure, dilated and hypertrophy cardiomyopathy, myocarditis and coronary artery disease, having a negative impact on the survival of HD and renal transplant patients [5,6].Intercellular Adhesion Molecule-1 (ICAM-1), or (CD54) is a type-I transmembrane proteinthat expressed at low levels on vascular endothelial cells, lymphocytes, monocytes and fibroblasts[7]. Elevated expression of this protein was revealed during different inflammatory processes, including CVDs, MI, angina, dyslipidemia, HCC and in patients with viral hepatitis[8, 9].Cardic Troponin-I (cTn-I) is a special protein complex located on the actin filamentsand was first described in the 1946 to be the regulator of the striated muscle contraction [10].Elevated levels of cTn-I were common in patients with CKD on HD procedure without significant myocardial damage. In other word, patients with CKD commonly have heart failure, which is associated with an elevated serum troponin in the absence of clinical myocardial ischemia or infarction [11]. N-Terminal pro-brain natriuretic peptide (NTpro-BNP) is a hormone found in brain tissue in 1988. Although it is produced in heart in small amounts, it is released in large amounts in response to changes in pressure inside the heart, supporting both arteries/veins volume expansion and fluid retention [12]. It is considered as a marker detects heart failure, indicating difficulties pumping sufficient amounts of blood to the body [13, 14].

Materials and Methods

Study Design and Population

This case-control study was carried out at the Department of Microbiology, College of Medicine, University of Baghdadduring the period between November 2020 till the end of April 2021. The study involved 90 participants regularly attended the Iraqi Center of Haemodialysis at Baghdad Teaching Hospital for scheduled HD, and data were collected from all of them via direct interview by the using of specially designed questionnaire. The participants were divided into two groups. The first was the patients group; involved 45 patients infected with HCV, the number of males was (24), whereas the number of females was (21). Age range24-74

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years. The second group was the control group; involved 45 patients clear from any viral existence (not infected), the number of males was (28), while the number of females was (17). Age range22-73 years.

Inclusion and ExclusionCriteria

Patients with CKD on HD procedure with/without HCV infection only and not presented with other diseases or medical conditions.Whereas the exclusion criteria involved patients with other diseases and/or other medical conditions and patients on antiviral treatment.

Laboratory Analysis

Blood specimens were collected from all the participants before HD session started. The biomarkers were measured in the serum of the participants by the using of Enzymelinked immunosorbent assay(ELISA) technique. The procedure was done according to a leaflet provided by the manufacturer.

Statistical analysis

Results were organized into tables and figures after being calculated with SPSS program version 16.0.0, Microsoft Excel 2010 and Graphpad Prism version 7.04.Both descriptive and inferential statistical analysis approaches were used to investigate or predict the relationships between variables, and a *P* value < 0.05 was considered to be statistically significant.

Results

The current study was aimed to define the possible role of HCV infection as a predisposing factor for CVDs among HD patients. The demographic data of the participants were shown in table (1). Total number of participants was 90; of them 52 (58%) were males and 38 (42%) were females. For the patients; the male to female ratio was (1.14:1) and the mean age was (58.26) years. Whereas for the control; the male to female ratio was (1.6:1) and the mean age was (53.37) years. Data analysis revealed that there wasno statistical significant difference between the age and sex of the participants.

Table (1): Demographic characteristics of the study samples

Demographic data	Rating and Scoring	Control	Patients	*P* value
Age (years)	**Mean± SD**	53.37±1.20	58.26±1.15	0.33 (NS)
	Range	53	50	
	22-32	2 (4)	3 (7)	0.08 (NS)
	33-43	5 (11)	5 (11)	
	44-54	7 (15)	18 (40)	
	55-65	19 (42)	13 (29)	
	66-75	12 (27)	6 (13)	
Sex	**Male**	28 (62)	24 (53)	0.655 (NS)
	Female	17 (38)	21 (47)	

NS: Non-significant association(*P*>0.05)

The level of ICAM-1 biomarker was detected in the current study, figure (1). The serum level of this biomarker among the control and the patients was 3.75 ± 1.85 and 6.44 ± 2.02, respectively, and a statistical significant difference was observed in the patients group in comparison to the control group.

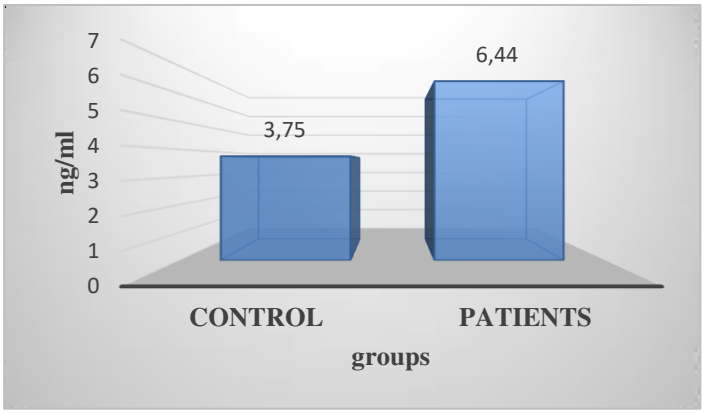

Figure (1): Comparison of mean ICAM-1 between control and patients

The levels of both NTpro-BNP and cTn-I biomarkers were determined in this study, table (2). Significant differences were found between the measured cardiac biomarkers in the patients group in comparison to the control group. The average levels of NTpro-BNP biomarker among the controls and the patients was 49.46 ± 19.47 and 86.95 ± 43.1, respectively, whereas for the cTn-I biomarker, the average levels among the controls and the patients was 278.91± 326.8 and 527.29 ± 445.5, respectively.

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Table (2): Mean and SD values of the measured cardiac biomarkers

Cardiac biomarkers	Control (N=45)		Patients (N=45)		*P* value
	Mean	SD	Mean	SD	
NTpro-BNP	49.46	19.47	86.95	43.1	**< 0.0001 (S)**
cTn-I	278.91	326.8	527.69	445.5	**0.003 (S)**

S: Significant association (*P*< 0.05)

Figure (2) revealed the correlation between each two-outcomes measurement among the patients group in comparison to the control group. **Figure (2A)** reveals strong significance positive linear correlation between Log. ICAM-1 concentration and Log. cTn-I among patients group with (R^2 = 0.2688) correlation and *P* value = 0.01. The correlation equation (Y= 114.22x–208.86) clarifies that an increase in one unit of ICAM-1 will lead to increase in cTn-I.**Figure (2B)** the dot graph shows a significance positive linear (R^2 = 0.0991) correlation between Log. ICAM-1 and Log. NTpro-BNP concentration among patients group with *P* value = 0.05. The correlation equation (Y= 6.7073+43.716) interpret that increasing in one unit of ICAM-1 will lead to an increase in NTpro-NBP.**Figure (2C)**, however, shows a significance positive linear correlation between Log. cTn-I concentration and Log. NTpro-BNP among patients group with (R^2 = 0.1252) correlation and *P* value = 0.05. The correlation equation (Y= 0.0342x+68.911) clarifies that an increase in one unit of cTn-I will lead to an increase in NTpro-NBP.

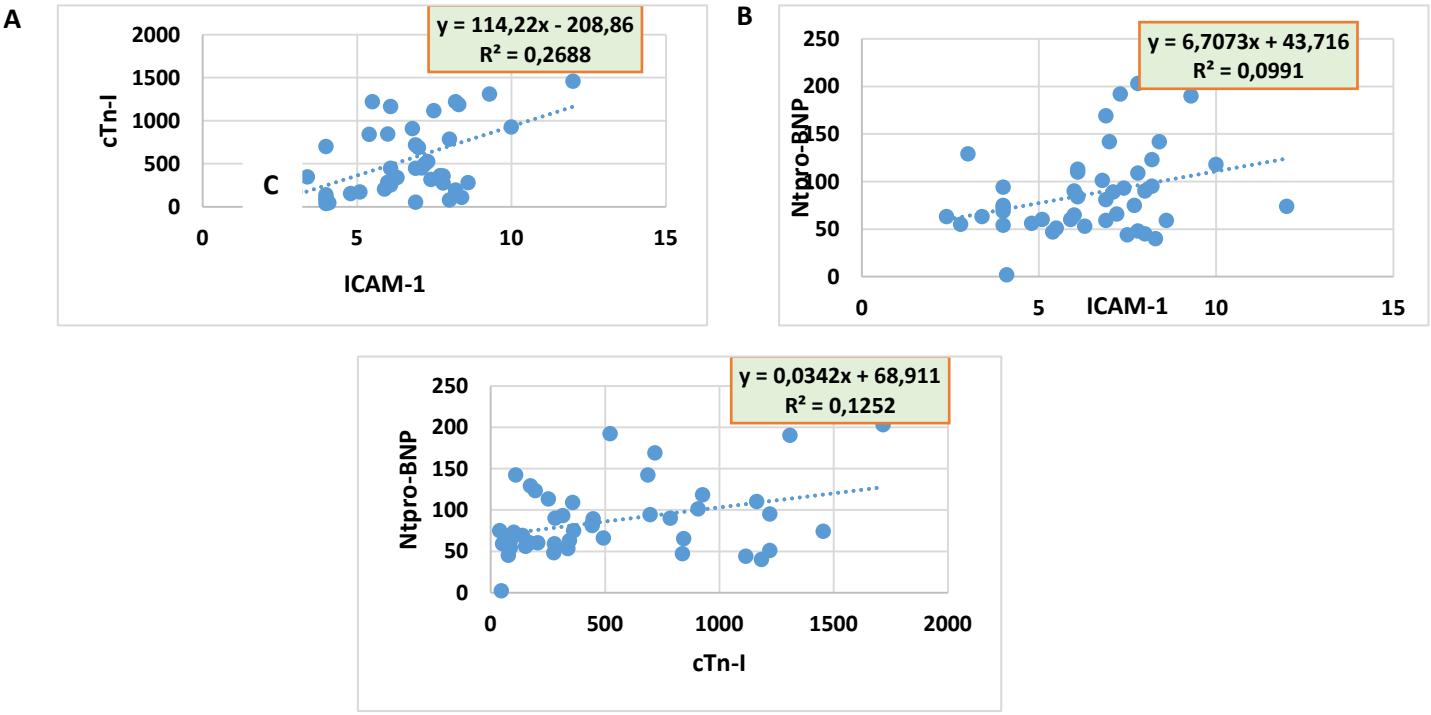

Figure (2):Correlation between each two-outcomes measurement among the patients group

Discussion

The purpose of the current study was to linked between the effect of HCV infection and the predisposition for CVDs among HD patients. The mean age of the participants was 55.8 years, which was in agreement with the fact that from the sixth decade (age 50-59 years) which is known also as the age of biological decline, people are predisposed to age-related diseases and their complications [15, 12]. Ageing is associated with an accumulation of different cellular and molecular damage over time, leading to a progressive reduction in physico-mental ability and predisposing for disease. These changes, however, are neither linear nor consistent [16]. Data analysis revealed that there was a higher statistical significant difference in the serum level of ICAM-1 among the patients group in comparison to the control group. These findings were in compatible with the findings of other studies done in Denmark [17], Saudia Arabia [9] and Iraq [18]demonstrated that in patients with HCV infection a significant positive increase in the serum levels of ICAM-1 was observed, which could be considered as an indicative marker of hepatic necrosis, inflammatory activity in CHC and a risk factor of CVDs events in HD patients. During inflammation, the ICAM-1 molecule plays an important role in the recruitment of white bold cells and increased levels might reflect to the endothelium dysfunction in CKD, leading to the initiation of atherosclerosis beside other atherogenic variables [19]. In patients with CKD on HD procedure, elevated serum levels of ICAM-1 might result from enhanced synthesis and releasing from endothelial cells stimulated by interlukin-1β and tumor necrosis factor-α proinflammatory cytokines, which were triggered and synthesized during HD by the contact of leukocytes with other exogenous challenges. Furthermore, chronic uremia in HD patients might also be associated with increased proinflammatory cytokines, leading to up-regulation release of this molecule [8, 20].

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Regarding cTn-I, which is a special protein inhibits ATPase activity of actinomyosin [21], it has been revealed that there was a highly statistical significant difference between the level of this biomarker in the patients group. The outcomes of this study were harmonious with studies done in Japan [22], Thailand [23] and India [24] documented that the infection with HCV could be an important predisposing factor for myocarditis, and cTn-I (through its elevated level) might be an effective prognostic marker for the detection of such complications, especially in patients with CKDs [22]. A study done in Italy in 2017 indicated that HD procedure does not significantly affect the serum levels of cTn-I, even when it was statistically significant [25]. Inconsistencies in results might be due to many reasons, including study design and variation in participants (since they were all on HD), geographic differences,assay used, certain conditions related to this infection, or due to the fact that patients with renal failure commonly have heart failure, which was associated with an elevated serum level of cTn-I without clinical MI. In other word, elevated levels of cTn-I were common in patients with CKDs on HD without significant myocardial damage [11].

On the subject of NTpro-BNP, which is a hormone released in response to pressure changes inside the heart and considered as a sensitive biomarker for cardiomyopathy [26], data processing shown that there was a higher statistical significant difference in the serum level among the patients in comparing to the control. These results were agreeing with the results of studies done in Japan [27, 28], Iran [29] and Egypt [26], demonstrated that HCV was found to be replicated in myocardial tissue of patients with myocarditis, leading to a higher release of NTpro-BNP and elevated serum level of this biomarker, thus, HCV infection may contribute to the development of this unusual form of myocarditis [27, 12]. A study done in Egypt in 2011 revealed that NTpro-BNP was a strong indicator of diastolic dysfunction in HCV patients and was directly related to ECG parameters changes, thus, it has been recommended for the measurement of this biomarker in the follow-up of these patients [30]. Moreover, it has been demonstrated that ESRD causes increased pulmonary arterial pressure and consequently right ventricular heart failure, leading to a higher levels of NTpro-BNP in this group of patients [28].

Conclusion

Patients with HCV infection have an increased risk of CVDs. Elevated serum levels of ICAM-1 endothelial function biomarker, cTn-I and NTpro-BNP cardiac dysfunction biomarkerswere seen among the patients in comparison to the control group. Positive correlations were demonstrated between the ICAM-1, cTn-I and NTpro-BNP biomarkersand between cTn-I and NTpro-BNP among the patients group. The findings of this study indicate the importance of regular screening of such important biomarkers among patients with haemodialysis in order to prevent the risk of such complications.

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Conflict of Interest. No conflict of interest.

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Ethical Clearance. Permission to conduct this study was issued by the Deanery of the College of Medicine/University of Baghdad and the Head of the Iraqi center of haemodialysis at Baghdad Teaching Hospital. The purpose and procedure were explained to the patients who gave us the approval to complete our work.

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