The impact of Hepatitis C Virus Load on cardiovascular risk factors in chronic renal failure patients on regular hemodialysis

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Abstract: Background: Chronic hepatitis C virus infection is associated with metabolic conditions such as insulin resistance, atherogenesis and increase the risk of cardiovascular diseases. **Methods**: Eighty participants considered eligible for the study, 60 patients with chronic renal failure on regular hemodialysis, had detectable HCV RNA and were considered to have chronic hepatitis C.The HCV +ve patients were divided into three groups according to PCR into low, moderate and high viremia. Compared with 20 patient on regular hemodialysis with no detectable RNA HCV as control, patients were predominantly having normal serum Calcium (8.5-10.5 mg/dL), Phosphorus: ≤ 5mg/dL PTH ≤250 pg/ml, Hb:10 -12 g/dL. All patients were subjected to full medical history, clinical examination, measurement of serum urea, creatinine, calcium, phosphorous, albumin,fasting blood glucose, blood picture, PTH, CRP and quantitative PCR for hepatitis C levels, ECG, echocardiography in addittion to measuring of carotid intimal thickness were done. **Results:** A significant increase in left ventricular mass index in hemodialysis patients with high and moderate viremia in comparison to low viremia P (< 0.001) and to control group P (< 0.001). A significant increase in end diastolic diameter in high and moderate viremia in comparison to low viremia and the control group (P< 0.001). **Conclusion:** Chronic hepatitis C virus infection is independently associated with the development of structural cardiovascular diseases such as LVMI. **Aim:** To clarify the association of HCV load with increased risk of cardiovascular diseases.

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Keyword: Hepatitis C Virus, cardiovascular risk, chronic renal failure patients, hemodialysis

1. Introduction:

The World Health Organization (WHO) estimates that global prevalence of HCV infection averages 3%.

HCV was recognized as the most important agent of liver disease among patients receiving long-term dialysis. As in the general population, the prevalence of HCV among dialysis patients varies worldwide, ranging from as low as 1% to as high as over 70%.[1]

Inflammation associated with chronic infections may contribute to the increased CV death risk in dialysis populations. HCV viraemia was *per se* associated with high pulse-wave velocimeter measurements and plays an atherogenic role through the aggravation of individual components of the metabolic syndrome.[2,3]

The precise pathogenic mechanisms connecting HCV infection, chronic liver disease, and atherogenesis are not completely understood. It is logical to hypothesize that HCV may promote atherogenesis through several direct and indirect biological mechanisms.[4]

2. Patients and Methods

Patient selection:

The study was conducted on 80 patients with chronic renal failure who are undergoing haemodialysis, divided in four groups:

-A control group with HCV negative by PCR (20 patients).

-Three HCV Positive groups according to viral load by PCR: low(n=16), moderate(n=30) and high viremia(n=14).

Methods

All patients were subjected to the following:

1- Complete history and physical examination.
2- Routine laboratory investigations complete blood count, erythrocyte sedimentation rate, serum urea, serum creatinine, and electrolytes

3-Quantitative PCR for hepatitis C levels

- Viral RNA isolation was performed according to manufacturer's instructions (QIAamp Viral RNA Mini Kit #52904 QIAGEN).
- The reaction mix (25ul) was consisted of:

12.5ul 2x RT-PCR buffer, 0.5 ul of each forward & Reverse primers, 0.5 ul of HCV probe, 1.5 ul PCR Grade water & 1 ul 25x RT-PCR enzyme & 8.5 ul of RNA sample.

- Cyclic conditions were: 45'C for 10 minutes, 95'C initial denaturation for 10 minuets & 50 cycles of denaturation at 95'C for 15 seconds & annealing and extension at 60'C for 45 sec.
- Data collection occurred at the end of Annealing and Extension step.

4-Assessment of parathormone level.

5- Transthoracic Echocardiography and calculation of LVMI

-Left ventricular mass calculation: (LVMI)

LVMI was determined by Devereux's formula: LVM = 1.04 × {[(LVIDd + PWT + SWT)3 − LVIDd3] − 13.6}. Subsequently LVM was divided by height$^{2.7}$ in order to evaluate the LVM index (LVMI) in terms of g/m$^{2.7}$. LVH was respectively defined as LVMI > 51 g/m$^{2.7}$ in men and > 47 g/m$^{2.7}$ in women.[5]

6- Carotid Duplex

Ultrasonographic studies on common carotid arteries where performed by using a 7.5 MHz high resolution probe. IMT was defined as a low-level echoic grey band that does not project into arterial lumen and was measured during end diastole as the distance from leading edge of the second echogenic line of the far walls of the initial tract of the internal carotid artery on both sides.

Statistical Analysis

Results were expressed as means ± standard deviation of the means (SD). Differences between groups were analyzed either by using the Chi square test or student's t test and non-parametric (Mann Whitney test) for comparison between two groups or ANOVA test for multiple group comparison. Spearman rank correlation coefficient was used to determine significant correlations among different parameters. The analysis was performed using Statistical Analysis System, version 6.03, on an IBM at personal computer.

1-SD: standard deviation.

2-M: mean.

3-P: P-value.

3. Results:

The demographic, clinical and laboratory data are summarized in tables 1,2 and 3 and Echocardiographic findings in different studied groups are presented in table 4.

Table 1: Etiology of renal failure in different studied groups.

	Control (N=20)	HCV group			P value
		Low (n= 16)	Moderate (n= 30)	High (n= 14)	
Unknown	4 (20%)	2 (12.5%)	6 (20%)	2 (14.3%)	0.091
DM	7 (35%)	6 (37.5%)	8 (26.7%)	6 (42.9%)	
GN	2 (10%)	2 (12.5%)	0 (0%)	4 (28.6%)	
HTN	6 (30%)	6 (37.5%)	8 (26.7%)	2 (14.3%)	
Polycystic kidney	1 (5%)	0 (0%)	2 (6.7%)	0 (0%)	
Urology	0 (0%)	0 (0%)	6 (20%)	0 (0%)	

Data are expressed as number (%).

Table 2: Demographic features of in different studied groups.

	Control (n= 20)	HCV group		
		Low (n= 16)	Moderate (n= 30)	High (n= 14)
Age	56.45 ± 8.85	56.88 ± 5.45	55.67 ± 11.23	56.57 ± 11.49
Gender (F/M)	4/16 (20%.80%)	8/8 (50%/50%)	8/22 (26.7%/73.3%)	10/4 (71.4%/28.6%)
Weight (kg.)	72.62 ± 14.14	77.25 ± 10.23	73.60 ± 13.31	69.57 ± 12.71
Height (m)	1.65 ± 0.06	1.63 ± 0.05	1.66 ± 0.08	1.64 ± 0.09
BMI	26.6 ± 4.7	29.03 ± 4.04	26.67 ± 4.54	25.69 ± 4.35
Duration of dialysis(months.)	7.35 ± 1.81	6.88 ± 1.31	6.33 ± 1.32	7.14 ± 1.70

Table 3: Biochemical profile in different studied groups.

	Control	Low	Moderate	High	P value
Ca	9.34 ± 0.59	9.34 ± 0.56	9.11 ± 0.37	9.44 ± 0.64	0.190
Ph	4.32 ± 1.05	4.34 ± 0.63	4.21 ± 0.73	4.16 ± 0.57	0.890
SGOT	20.05 ± 9.26	17.62 ± 7.23	15.4 ± 5.87	19.43 ± 8.32	0.149
SGPT	28.3 ± 10.33	30.88 ± 12.31	28.0 ± 18.22	37.29 ± 17.57	0.278
ALP	204.65 ± 112.85	153.38 ± 80.91	175.6 ±110.99	209.14 ± 95.01	0.366
Urea	127.35 ± 15.80	112.12 ± 15.81	119.67 ± 22.38	126.71 ± 19.60	0.082
Creatinine	7.33 ± 1.13	7.5 ± 0.68	7.91 ± 0.73	7.73 ± 1.06	0.142
Hb	10.78 ± 0.43	10.85 ± 0.59	10.69 ± 0.52	10.5 ± 0.39	0.251
PTH	168.1 ± 53.224	187.12 ± 53.29	185.87 ± 44.33	172.29 ± 29.97	0.476

Table4. Echocardiographic findings in different studied groups.

	Control	Low	Moderate	High	P value
LVMI	43.94 ± 10.93	59.61 ± 5.89 [a]	63.52 ± 6.76 [a]	79.01± 13.68 [abc]	0.001**
Ao	28.7 ± 4.94	27.75 ± 3.72	28.8 ± 5.11	31.86 ± 3.53	0.089
LA	37.5 ± 7.04	39.88 ± 7.07	39.4 ± 6.43	43.43 ± 5.65	0.088
EDD	44.65 ± 10.91	51.88 ± 4.43 [a]	49.0 ± 3.17 [a]	59.29 ± 5.59 [abc]	0.001**
ESD	31.85 ± 4.80	33.25 ± 4.16	32.07 ± 2.53	40.0 ± 7.19 [abc]	0.001**
FS	37.95 ± 10.68	39.0 ± 8.26	37.87 ± 7.37	33.29 ± 6.12	0.250
EF	64.35 ± 9.35	61.12 ± 13.36	63.4 ± 11.19	60.43 ± 9.08	0.679
PWTd	11.0 ± 2.25	11.12 ± 1.31	12.67 ± 1.27 [ab]	12.0 ± 1.84	0.003**
IVSTs	15.0 ± 2.47	16.25 ± 3.13	18.07 ± 1.84 [ab]	16.71 ± 2.27 [a]	0.001**
PWTs	15.55 ± 2.98	16.62 ± 2.13	16.93 ± 1.72	16.86 ± 1.61	0.149
IMT	1.08 ± 0.17	1.12 ± 0.12	1.09 ± 0.22	1.13 ± 0.13	0.784

Data are expressed as mean ± SD or number (%).
p< 0.01= highly significant.
[a] p< 0.01 relative to control group.
[b] p< 0.01 relative to low group.
[c] p< 0.01 relative to moderate group.

There was a statistical significant difference between studied groups regarding LVMI (left ventricular mass index), 79.01±13.68 in high viremia group vs control group 43.94 ± 10.93, Low viremia group 59.61 ± 5.89 and moderate viremia group 63.52 ± 6.76,EDD (end diastolic diameter) 59.29 ± 5.59 in high viremia group vs control group, 44.65 ± 10.91, Low viremia group 51.88 ± 4.43 and moderate viremia 49.0 ± 3.17, ESD (end systolic diameter) 40.0 ± 7.19 in high viremia group vs control group 31.85 ± 4.80, Low viremia group 33.25 ± 4.16 and moderate viremia 32.07 ± 2.53 and IVST (interventricular septal thickness) 16.71 ± 2.27 in high viremia group vs control group 15.0 ± 2.47.

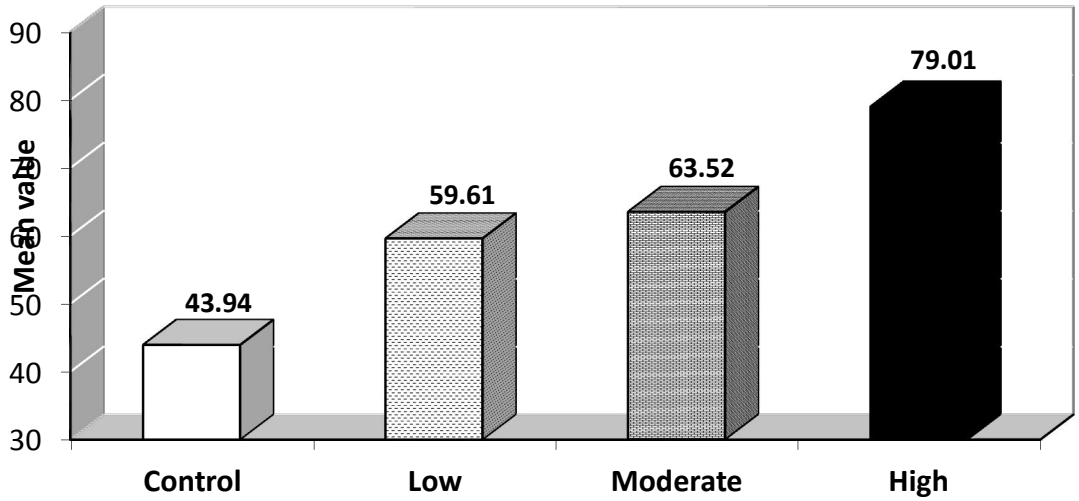

Fig 1: Mean values of LVMI in different studied groups

4. Discussion

Cardiovascular complications are the leading cause of mortality in patients with ESRD. Complications include coronary artery disease, left ventricular hypertrophy, heart failure and arrhythmia. Although traditional risk factors, such as diabetes mellitus, hypertension and dyslipidemia are prevalent in ESRD. They are not sufficient to account for the high prevalence of cardiovascular mortality, thus the search for other nontraditional risk factors that may be involved in pathogenesis of uremia is under intense study.

In our study there is a significant increase in left ventricular mass index in hemodialysis patients with high and moderate viremia in comparison to low viremia P (< 0.001) and to control group P (< 0.001). In agreement with our results high prevalence of hepatitis C virus (HCV) infection has earlier been noted in patients with hypertrophic cardiomyopathy, dilated cardiomyopathy, and myocarditis. In this issue of, Omura et al reported that mice transgenic for the HCV-core gene develop ventricular dilatation, cardiac dysfunction, and myocardial fibrosis at 12 months, similar to the pathological manifestations observed in human dilated cardiomyopathy. Although HCV infection may be the cause of several phenotypically different cardiomyopathies, mild inflammation with mononuclear cell infiltration has also been observed with HCV infection in humans. However, no lymphocytic infiltration was observed in these HCV-core transgenic mice. Furthermore, cardiomyocyte hypertrophy and disarray of the myofibers are typical characteristics of human hypertrophic cardiomyopathy, but the wall thickness of the HCV-core mice was not increased. [7,8]

A significant increase in end diastolic diameter in high and moderate viremia in comparison to low viremia and the control group (P< 0.001), and a significant difference in end systolic diameter in the high viremia group in comparison to the low, moderate viremia and the control group(P< 0.001) was found in our study.

The pathogeneses of HCV hepatitis and cardiomyopathies are compared in HCV liver disease, most patients develop chronic hepatitis and years later, liver cirrhosis, hepatic failure, or hepatocellular carcinoma. In HCV heart disease, most patients develop chronic inflammation of the myocardium and later, dilated cardiomyopathy attributable to necrosis and loss of myocytes. However, because myocytes do not replicate, proliferative stimuli induced by HCV infection may promote myocyte hypertrophy and hypertrophic cardiomyopathy [9].

Our results also showed a significant increase in interventricular septal thickness

(P<0.002), posterior wall thickness (P< 0.002) in moderate viremia versus low viremia and control group.

Appart from renal disease patients, overall 364,712 individuals who underwent investigation for any potential association between HCV infection and cardiovascular disorders in 31 studies have been reviewed in a systematic review, 6 out of 31 reviewed studies involving a cumulative population of 81,035 (22.2%) subjects reported a negative association between HCV infection and cardiovascular disorders. There were 2 prospective studies, both in favor of a significant relation between HCV infection and cardiovascular disease [12]

However, our data showed no significant difference in carotid intimal thickness between the studied groups. Conflicting literature data have reported either normal or increased IMT, and normal or increased prevalence of carotid artery plaques in patients with a clinical diagnosis of HCV infection compared with populations. In keeping with a potential association between HCV infection and atherosclerotic disease, studies have highlighted that HCV seropositivity was an independent predictor of increased coronary atherosclerosis.

patients with histologically diagnosed G1 CHC, study found that G1 CHC patients had higher IMT compared with a comparable control population novel finding is the independent association of the presence of carotid plaques with severe hepatic fibrosis, after adjustment for age. Similarly, it was also found an independent association of IMT with low platelet count, an expression of more advanced fibrosis[10,11]

studies demonstrated the presence of genomic and antigenomic HCV RNA strands within carotid plaque tissues in HCV-infected patients. In addition, the proinflammatory and profibrogenic environment prompting fibrogenesis in the liver of HCV-infected patients could also be systemically activated, enhancing the development of atherosclerotic lesions, explaining the higher prevalence of carotid plaques in this subgroup of CHC patients. Patients with chronic hepatitis C had more hypertension, higher glycosylated hemoglobin level and a higher prevalence of metabolic syndrome. Patients with chronic hepatitis C had increased hsCRP (high-sensitivity C-reactive protein), sICAM-1 (soluble intercellular adhesion molecule-1), sVCAM-1 (soluble vascular cell adhesion molecule-1), and soluble E-selectin. [10,11]

However our results shows no direct association was found between viral load and atherosclerosis, probably due to the fluctuating levels of viremia in HCV infection, also,studies found lower levels of tPAI-1 (tissue-type plasminogen activator inhibitor-1), MMP9 (matrix metallopeptidase 9), and MPO (myeloperoxidase) than their comparisons. In addition, those with chronic hepatitis C had less dyslipidemia (including significantly lower low-density lipoprotein and cholesterol/high-density lipoprotein ratio. In agreement of our data caliskan etal., stated that hepatitis c virus infection in hemodialysis patients is not associated with insulin resistance, inflammation and atherosclerosis. Since hemodialysis patients had a large number of cardiovascular risk factors, the effect of HCV infection could be not obvious. [6]

Our data suggests that HCV have a significant effect on the development of structural cardiovascular diseases in the general population, and in renal disease patients. There is data scarcity on the impact of HCV infection on aortic atherosclerosis in the general population, and both of the available studies are on renal disease patients. We suggest prospective cohort studies with more controlled conditions.

Conclusions:

Chronic hepatitis C virus infection is independently associated with the development of structural cardiovascular diseases such as LVMI.

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