Global Advanced Research Journal of Medicine and Medical Science (ISSN: 2315-5159) Vol. 4(10) pp. 435-440, October, 2015
Available online http://garj.org/garjmms

Full Length Research Paper

Study of Increased Atherosclerosis Risk In Hepatitis C virus and Cytomegalovirus Seropositive Haemodialysis Patients

Ghada Al-Ghazaly[1]* and Tarek El-Sharawy[2]

[1]Lecturer, Internal Medicine Department, Faculty of medicine, Tanta University, Egypt.
[2]Assistant Professor, Internal Medicine Department, Faculty of medicine, Tanta University, Egypt.

Accepted 02 October 2015

Hepatitis C virus (HCV) is the most common liver disease in renal dialysis patients. Also, cytomegalovirus (CMV) is a common infection in chronic hemodialysis patients (CHD). HCV and CMV patients are more likely to have carotid atherosclerosis plaques as compared to negative individuals. The aim of this study is to assess the association between HCV and CMV seropositivity, dyslipidemia, carotid artery plaques and media intima thickening in hemodialysis patients. Sixty patients with chronic kidney disease (CKD) on regular hemodialysis were selected from hemodialysis unit in Tanta university hospital. All subjects were subjected to medical history taking, physical examination, complete blood picture (CBC), fasting blood glucose (FBS), liver function tests, lipid profile, serum calcium, serum phosphorus, INR, prothrombin concentration , C-reactive protein (CRP), HCV Ab (ELISA) and CMV IgG and Duplex on both Carotid arteries with measurement of intimal medial thickness. The prevalence of atherosclerosis in HCV, CMV positive and negative patients undergoing hemodialysis is not influenced by many factors (p value >0.05): sex, age, and body mass index, systolic and diastolic blood pressure, Also there was no significant change in serum albumin, bilirubin, prothrombin concentration, INR, CBC, FBS, CRP, serum phosphorus and ionized calcium. There was significant increase in atherosclerosis among HCV and CMV positive compared to negative patients undergoing hemodialysis as proved by Carotid Duplex. Atherosclerosis is increased in HCV and CMV seropositive compared to seronegative patients under hemodialysis as proved by Carotid Duplex.

Keywords: Hepatitis C virus, cytomegalovirus, Haemodialysis, Atherosclerosis, Carotid Duplex, Risk factors

INTRODUCTION

More than 50 % of end-stage renal disease (ESRD) patients die from cardiovascular diseases (Collins, 2003). Arteries of ESRD patients are affected by atherosclerosis and by large artery (medial and intimal) calcifications (Ballanti et al., 2011). Many risk factors have been identified, they include traditional risk factors known from the non-ESRD population (diabetes mellitus, smoking, hypertension etc.), but also factors specific for renal failure, such as increased phosphate concentrations, inflammation, oxidative stress, malnutrition and increased levels of circulating ADMA (asymmetric dimethyl-arginine, endogenous inhibitor of nitric-oxide synthase). Despite these findings, the use of traditional risk scoring underestimates atherosclerosis burden (Coll et al., 2010).

*Corresponding Author E-mail: dodoya288@yahoo.com

Hepatitis C virus (HCV) is a disease with a significant global impact. According to the World Health Organization there are 130-170 million people infected with HCV. There are considerable regional differences. In some countries, e.g., Egypt, the prevalence is as high as 22% (WHO 2011), the prevalence of HCV antibodies in hemodialysis patients ranging from 52.3 to 82.3% (Afifi et al., 2008). HCV patients are more likely to have a higher likelihood of having carotid atherosclerosis plaques as compared to HCV negative individuals (Aslam et al., 2010).

Cytomegalovirus (CMV) is a β-herpes virus and known to be present in saliva, cervical secretions, breast milk, semen, and human lymphocytes. CMV is a ubiquitous agent, and seropositivity rates in the adult population over 40 years of age worldwide are 60 to 100%, possibly due to transmission through breastfeeding, sexual contact and spread from children (Hecht et al., 2006). Transfusion-transmitted CMV infection is a significant cause of morbidity and mortality, particularly in immunocompromised patients (Nassetta et al., 2009).

CMV seropositivity is likely to play a role as an atherosclerosis-promoting factor in an already diseased vascular system, such as the arteries of patients with ESRD (Stassen et al., 2006).

The aim of this study is to assess the association between HCV and CMV seropositivity, dyslipidemia, carotid artery plaques and media intima thickening in hemodialysis patients.

PATIENTS AND METHODS

The present study is a cross-sectional study. It was conducted in the period extending from June, 2013 through June, 2014. This study included 60 patients on dialysis for at least 6 months or more. From the dialysis unit of the internal medicine department Tanta university hospital.

Exclusion criteria: Patients who are suffering from Diabetes Mellitus, ischemic cardiac disease, receiving cholesterol lowering medications, with a history or other evidence of angina, previous myocardial infarction, previous stroke.

Subjects reported to the Dialysis Unit after a 12-h overnight fast. All subjects were subjected to: **a) Medical History:** Including age, sex, residence, level of education, occupation, marital state and special habits. **b) Physical examination:** Including revision of all systems and three consecutive measurements of sitting blood pressure were recorded. Systolic and diastolic blood pressures were computed as the mean of the three measurements. **c) Anthropometric measurements:** Weight was measured to the nearest 0.5 kg and height to the nearest 1.0 cm and basal metabolic index (BMI) was calculated as body weight in kilograms divided by the square of height in meters (kg/m2).**d) Laboratory investigations:** Complete Blood Picture (CBC), Fasting blood glucose (FBG), Liver function tests (ALT [SGPT], AST [SGOT], T.Bilirubin, and S.Albumin), Lipid profile (Triglycerides, total cholesterol, HDL, LDL), Serum calcium, serum phosphorus, Parathormone Hormone (PTH), Prothrombine time (PT), Partial Thromboblastin time (PTT), INR , C-reactive protein (CRP), HCV Ab (ELISA) and CMV IgG.

Radiological investigation

Carotid artery duplex for evaluation of common carotid artery intima-media thickness (CCA-IMT) was measured by high-resolution B-mode ultrasonography. Ultrasonographic study of patients was performed after dialysis within one week of blood sampling. Bilateral examination was done by an expert radiologist who was unaware of clinical and laboratory data. Subjects were in the supine position with head slightly turned from echography at measurement. Measurement of IMT was performed 0.5 to 1.0 cm proximal to the beginning of the carotid bulb on the wall of the CCA. IMT was defined as the distance between the leading edge of the lumen-intima echo of the near wall and the leading edge of the media adventitia echo. IMT was measured on longitudinal views of the far wall of the distal segment of the CCA. Mean values of IMT were calculated from at least three measurements for each artery. The average of the obtained values was taken as IMT; it was considered abnormal when it exceeded 0.8 mm.

Statistical analysis

Data obtained from the present study were computed using SPSS versions 17 under the platform of Microsoft Windows 7. Continuous data were expressed in the form of mean ± SD while categorical data were expressed in the form of count and percent. Comparison of continuous data was performed utilizing student t test, while categorical data were done using Chi-square test. Relation between variables were investigation by Pearson's correlation coefficient. P value less than 0.05 was considered statistically significant.

RESULTS

Table 1. This table shows that among the studied patients 80.0 %, 33.3 % were CMV +ve and HCV +ve respectively.

		No	%
CMV	**+ve**	48	80.0
	-ve	12	20.0
HCV	**+ve**	20	33.3
	-ve	40	66.7

Table 2. show some laboratory data in the studied patients

	Range	Mean ± SD
AP	352.0 - 450.0	393.7 ± 28.1
Albumin	2.8 - 4.6	3.6 ± 0.5
PTH	254.0 - 1050.0	482.5 ± 149.2
CRP	3.5 - 17.5	10.1 ± 3.9
Cholesterol	180.0 - 250.0	215.9 ± 18.3
Triglycerides	110.0 - 658.0	316.1 ± 167.8
HDL	19.0 - 64.0	37.3 ± 12.3
LDL	5.0 - 199.8	115.3 ± 41.4

Table 3. This table shows that the studied patients had an IMT of 0.91 ± 0.38 and they included 25 patients (41.7 %) with atherosclerosis.

IMT	**Range**	0.5 – 1.7
	Mean ± SD	0.91 ± 0.38
Atherosclerosis	**+ve**	25 (41.7 %)
	-ve	35 (58.3 %)

Table 4. This table shows no statistically significant differences between patients with CMV and without regarding HCV infection.

	CVM +ve n=48	CMV –ve n=12	Chi-square test X^2	P
HCV +	18	2	1.87	0.17
HCV -	30	10		

Table 5. This table shows that patients with HCV had significantly higher IMT and frequency of atherosclerosis when compared with patients without.

	HCV +ve n=20	HCV –ve n=40	Student t test t	p
IMT	1.29 ± 0.29	0.72 ± 0.27	7.4	0.0001*
			Chi-square test X^2	**P**
Atherosclerosis +ve	19	6	35.1	0.0001*
Atherosclerosis –ve	1	34		

Table 6. This table shows that patients with CMV had significantly higher IMT and frequency of atherosclerosis when compared with patients without.

	CVM +ve n=48	CMV –ve n=12	Student t test t	P
IMT	0.97 ± 0.39	0.68 ± 0.27	2.39	0.02*
			Chi-square test X^2	P
Atherosclerosis +ve	24	1	6.8	0.009*
Atherosclerosis –ve	24	11		

Results also revealed the presence of atherosclerotic plaque in the righ common carotid artery (4.01 × 11.2 mm) confirmed by colored Carotid Duplex

DISCUSSION

In the present study, it was shown that among the studied patients, 20 patients were HCV +ve (33.3 %) while the remainder 40 (66.7 %) were HCV –ve. This figure is close to that found by *Khodir et al., (2012)* who estimate the prevalence of anti-HCV positive patients in its different HD units in Al Gharbiyah Governorate, Egypt; they found that 824 out of 2351 patients (35%) were anti-HCV reactive (Khodir et al., 2012).

In addition, we found that studied patients had an IMT of 0.91 ± 0.38 and they included 25 patients (41.7 %) had atherosclerosis. This is in agreement with *Balsam et al., (2009)*. In their study, 40.0 % of HD patients had IMT > 0.8 mm (Balsam et al., 2009).

In the present study, CMV IgG was found to be positive in 48 patients (80.0 %). This is in accordance with the study of *Sepehrvand et al., (2010)* they found that forty-four (52%) patients were males. 65 patients (77.4%) were anti-CMV IgG positive and 6 (7.1%) were anti-CMV IgM positive (Sepehrvand et al., 2010). This also accords with the study of *Betjest et al., (2009)* who found that among the studied HD patients 73.8 % were CMV +ve (Betjest et al., 2009).

On the other hand, *Abou-El-Yazed et al., (2008)* found that the seroprevalance of CMV antibodies among their patients was 98% using CMV/IgG, 11% using CMV/IgM and 30% by using CMV/Ampilcor (PCR) (Abou-El-Yazed et al., 2008).

Also, *Ocak et al., (2006)* found the Positivity for anti-CMV IgG was in 254 (99.6%) of the 255 HD patients so this is in accordance with the result of the present study (Ocak et al., 2007).

In addition, no significant associations were found between CMV and HCV infection and the various clinical and laboratory data. However, it was found that patients with CMV and HCV had significantly higher IMT and frequency of atherosclerosis when compared with patients without.

This is in agreement with the study of *Betjes et al., (2009)*. In a retrospective study they analysed the clinical data of patients with ESRD. A total of 408 patients were evaluated with a median age of 52 years. Multivariate logistic regression identified age, smoking, hypertension, CRP and CMV seropositivity as independent variables that were significantly associated with a positive medical history of atherosclerotic disease (Betjest et al., 2009).

However, the present data are in disagreement with the study of *Buyukhatipoglu et al., (2007)* who evaluated the causative role of inflammation in atherosclerosis among HD patients. Intima-media thickness (IMT) in carotid arteries was determined in 54 HD patients and 52 controls. Plasma levels of lipids, glucose, albumin and several acute phase proteins, and immunoglobulin G titters against Chlamydia and cytomegalovirus were measured in all subjects. There was no relationship between carotid IMT and cytomegalovirus (Buyukhatipoglu et al., 2007).

Also is against the present study; *Wolf et al., (2004)* evaluated whether there is a correlation between a past infection with Chlamydia pneumonia (Cpn), Helicobacter pylori (Hp) or CMV and the manifestation of a symptomatic atherosclerotic disease in patients with end stage renal failure, they found that There was no correlation between CMV (IgG, IgM) or Hp (IgA, IgG) seropositivity and atherosclerotic disease (Wolf et al., 2004).

Boddi et al., (2007) found that HCV infection may be localized in plaque tissue, accordingly, the detection of viral RNA in the plaque tissue of patients in the absence of detectable viremia points out the possibility of a compartmentalization of the virus in this district with pathogenetic consequences. This in turn suggests a role of HCV in carotid atherogenesis (Boddi et al., 2007).

Adinolfi et al., (2012) observed that also viral load and hepatic steatosis are associated with the presence of carotid atherosclerosis in CHC subjects, thus assuming that HCV infection could be a relevant risk factor for carotid atherosclerosis occurrence via viral load and steatosis (Adinolfi et al., 2012).

In agreement with the presnt study results *Ishizaka N et al., 2002* stated that sero positivity for HCV hows a positive association with carotid artery plaque and carotid intima-media thickening, independent from other risk

factors for atherosclerosis (Ishizaka et al., 2002).

Results of the present study also are in agreement with *(Adeel et al., 2009)* who found that HCV infected subjects were at a significantly higher risk of developing atherosclerosis, compared with HCV-uninfected subjects. The reason for the increased risk is unclear but recent studies support the role of inflammation in the pathogenesis of atherosclerosis. According to these studies, a complex balance between pro-inflammatory and anti-inflammatory cytokines dictates the initiation, propagation, and rupture of atherosclerotic lesions. Some studies have shown that the levels of inflammatory markers (e.g., high sensitivity CRP, interleukin 6, and tumor necrosis factor TNF-|α|) are higher in HCV (Adeel et al., 2009).

On the contrast, a recent population-based Japanese study showed a paradoxically lower risk of atherosclerosis in CHC patients compared with healthy controls, even if an increased prevalence of insulin resistance (IR) in patients with HCV infection is confirmed (Miyajima et al., 2013). Also, in a large population study from Northern Europe, HBV and HCV infections were not associated with an increased risk for cardiovascular events, including carotid atherosclerosis, myocardial infarction, and stroke (Völzke et al., 2004).

Infected subjects compared with HCV-uninfected control subjects. In the present study we found that hypercholesterolemia is predictor of atherosclerosis in the studied patients.

However, the present data are in disagreement with the study of *Cheung AK et al., (2000)* who examined the relationship between several traditional cardiovascular disease risk factors and the presence or history of cardiovascular events in hemodialysis patients, they found that forty percent of the patients had coronary heart disease. Nineteen percent had cerebrovascular disease, and 23% had peripheral vascular disease. As expected, diabetes and smoking were strongly associated with cardiovascular diseases. Increasing age was also an important contributor, especially in the group less than 55 years and in non diabetic patients. Black race was associated with a lower risk of cardiovascular diseases than non-blacks. Interestingly, neither serum total cholesterol nor pre-dialysis systolic blood pressure was associated with coronary heart disease, cerebrovascular disease, or peripheral vascular disease (Cheung et al., 2000).

This study is in agreement with (Mustafa et al., 2012) whose study showed that albumin is inversely and independently associated with CIMT of haemodialysis patients (Mustafa et al., 2012).

This study is in variance with (Nassiri et al., 2012) could not detect an association between serum levels of calcium, phosphorus, parathyroid hormone, and 25-hydroxyvitamin D and atherosclerosis (Nassiri et al., 2012).

CONCLUSION

In conclusion**,** The infection with both HCV and CMV increases the risk of atherosclerosis in patient with chronic renal failure on dialysis, so infection control is very important to avoid adding risk factors to those patients for morbidity and mortality.

REFERENCES

Abou-El-Yazed E, El-Hoseny IM, Kasim K, et al (2008**).** Prevalence of cytomegalovirus infection among patients undergoing hemodialysis. Egypt J. Immunol. *15(2):33-41*.

Adeel A Butt, Wang Xiaoqiang, Matthew Budoff, et al (2009). Hepatitis C Virus Infection and the Risk of Coronary Disease. *Clin. Infect. Dis. 49 (2): 225-232.*

Adinolfi LE, Restivo L, Zampino R, et al (2012). "Chronic HCV infection is a risk of atherosclerosis. Role of HCV and HCV related steatosis," *Atherosclerosis*, 221(2): 496–502.

Afifi A, et al (2008). Annual reports of the Egyptian renal registry; 1996-2008, http://www.esnonline.net.

Aslam F, Alam M and Lakkis NM (2010). Hepatitis C virus and carotid atherosclerosis: a retrospective analysis. *Atherosclerosis*. 209: 340-343.

Ballanti P, Silvestrini G, Pisanò S, et al (2011). Medial artery calcification of uremic patients: a histological, histochemical and ultra structural study. *Nephrol. Dial Transplant*. 26: 349-357.

Balsam, Mohsen M. EL Kossi, Robert Lord, et al (2009). Cardiovascular disease on hemodialysis: Predictors of atherosclerosis and survival Hemodialysis International. 13(3): 278–285.

Betjest MGH, Weimar W, Litjens NHR (2009). CMV seropositivity determines epoetin dose and hemoglobin levels in patients with CKD. J. Am. Soc. Nephrol. *20:2661-2666*

Boddi Rosanna Abbate, Benedetta Chellini, et al (2007). HCV infection facilitates asymptomatic carotid atherosclerosis, digestive and liver suppl. *S43-S39*

Buyukhatipoglu H, Tiryaki O, Tahta K, et al (2007). Inflammation as a risk factor for carotid intimal-medial thickening, a measure of subclinical atherosclerosis in haemodialysis patients: the role of chlamydia and cytomegalovirus infection. J. Nephrol. (Carlton). *12(1):25-32.*

Cheung AK1, Sarnak MJ, Yan G, et al (2000). Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int. *58(1):353-362.*

Coll B, Betriu A, Martinez-Alonso M, et al (2010). Cardiovascular risk factors underestimate atherosclerotic burden in chronic kidney disease: usefulness of non-invasive tests in cardiovascular assessment. *Nephrol. Dial Transplant*. 25: 3017-3025.

Collins AJ (2003). Cardiovascular mortality in endstage renal disease. *Am. J. Med. Sci. 325*: 163-167.

Hecht HS, Budoff MJ, Berman DS, et al (2006). Coronary artery calcium scanning: clinical paradigms for cardiac risk assessment and treatment. Am. Heart J. *151:1139-1146.*

Ishizaka N, Ishizaka Y, Takahashi E, et al (2002). Association between hepatitis C virus seropositivity, carotid-artery plaque, and intima-media thickening. *Lancet.* 359:133-135.

Khodir SA, Alghateb M, Okasha KM, et al (2012). Prevalence of HCV infections among hemodialysis patients in Al Gharbiyah Governorate, Egypt. *5(3):145-147*.

Miyajima T, Kawaguchi A, Fukami, et al (2013). "Chronic HCV infection was associated with severe insulin resistance and mild atherosclerosis: a population-based study in an HCV hyperendemic area," *J. Gastroenterol*. 48:93–100.

Mustafa Duran, Aydin Unal, Mehmet Tugrul Inanc, et al. (2012). Changes in carotid intima-media thickness over two years in patients on haemodialysis. *J. Pak. Med. Assoc*. 62(6).

Nassetta L, Kimberlin D, Whitley R (2009). Treatment of congenital cytomegalovirus infection: implications for future therapeutic strategies. J. Antimicrob. Chemother. *63:862–867.*

Nassiri Amir Ahmad, Monir Sadat Hakemi, Reza Asadzadeh, et al (2012). Differences in Cardiovascular Disease Risk Factors Associated With Maximum and Mean Carotid Intima-Media Thickness Among Hemodialysis Patients. *Iranian J. Kidney Dis. 6(3).*

Ocak S, Zeteroglu S, Ozer C, et al (2007). Seroprevelance of Toxoplasma gondii, rubella and cytomegalovirus among pregnant women in southern Turkey. Scand. J. Infect. Dis. *93(3):231-234*

Sepehrvand, Zakieh Rostamzadeh, Hamid-Reza Farrokh (2010). Survey the seroprevalence of CMV among hemodialysis patients in Urmia, Iran, *21-2-363-367*.

Stassen FR, Vega-Co´ rdova X, Vliegen I, et al (2006). Immune activation following cytomegalovirus infection: More important than direct viral effects in cardiovascular disease? J. Clin. Virol. *35: 349–353*.

Völzke C, Schwahn B, Wolff, et al (2004). "Hepatitis B and C virus infection and the risk of atherosclerosis in a general population," *Atherosclerosis*, 174(1): 99–103.

Wolf SC, Brehm BR, Mayer O, et al (2004). Infectious risk factors for atherosclerotic vascular disease in hemodialysis patients--Chlamydia pneumoniae but not Helicobacter pylori or cytomegalovirus is associated with increased C-reactive protein. *26(3):279-287.*