EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 2
Issue: 7
01-04
Year: 2015

MONOCYTE CHEMOATTRACTANT PROTEIN-1 (MCP-1): A NOVEL MARKER FOR ARTERIOVENOUS FISTULA FAILURE.

Gamal A.Tawfik (MD), Fawzy A. Khalil (MD), Seham A. Omar (MD), Mohammed M. Keshawy (Msc) and Hamdy Sliem(MD)*

Department of internal Medicine, Faculty of Medicine, Suez Canal University, Egypt.

***Author for Correspondence: Hamdy Sliem(MD)**
Faculty of Medicine, Suez Canal University, Egypt.

Article Received on 23/09/2015 **Article Revised on 15/10/09/2015** **Article Accepted on 01/11/2015**

ABSTRACT

Background

Emerging evidences suggest that inflammation is involved in the pathogenesis of cardiovascular diseases. Monocyte chemoattractant protein-1 (MCP-1) has a central role in atherogenesis. The study was performed as a cross sectional study aiming at determining the role of MCP-1 in hemodialysis (HD) induced inflammation and dyslipidemia in relation to arteriovenous fistula (AVF) failure among end stage renal disease (ESRD) patients. **Methods:** 90 patients in Ismailia governorate, Egypt were enrolled in the study. Predialysis and postdialysis MCP-1 gene expression, CRP and lipid profile were done in addition to standard laboratory work up for ESRD patients. **Results:** The patients` mean age was 46.35 years, 63.33 % were males**.** Predialysis MCP-1 , postdialysis MCP-1 and predialysis CRP levels are significantly higher in patients who had experienced arteriovenous fistula (AVF) failure. **Conclusion:** MCP-1 can be used as a marker for dialysis induced inflammation and AVF failure.

KEYWORDS: MCP-1, ESRD and AVF failure.

Abbreviations: Arteriovenous fistula (AVF); End stage renal disease (ESRD); Monocyte chemoattractant protein-1 (MCP-1); C- reactive protein (CRP).

INTRODUCTION

Inflammation is important in the pathogenesis and progression of atherosclerotic disease. MCP-1 is a pre-inflammatory cytokine which works on blood vessel endothelium changes. It is synthesized by various cells associated with atherosclerosis, including endothelial cells, muscle cells, fibroblasts, and macrophages.[1] Over the past two decades, overwhelming accumulated evidences have supported the key role of MCP-1 in the development of atherosclerosis.[2] In addition**,** Serum levels of MCP-1 are increased in ESRD patients as a result from either inadequate clearance or enhanced synthesis and release.[3] Hemodialysis session may result in a significant increase of the MCP-1 blood levels but the exact mechanisms responsible for these alterations are yet to be fully elucidated. The influence of the HD membranes on their secretion had been suggested. In addition, both modified cellulose and polysulfone membranes resulted in a significant and comparable increase of these molecule levels after correcting for hemoconcentration.[4] The up-regulation of MCP-1 not only represents a mechanism for cardiovascular disease but also accounts for the failure of an AVF. Subsequently, hemodialysis AVF dysfunction may reflect, in part, the overarching propensity for cardiovascular disease imposed by the uremic milieu.[5]

Failure of an AVF is driven by increased expression of MCP-1 -which has a fundamental importance in cardiovascular diseases- may occur with heightened frequency in chronic kidney disease.[6] Another cause of over expression is that, MCP-1 mRNA expression is regulated by hemodynamic stress. Thus tempting to speculate that such consistent up-regulation of MCP-1 in the venous vasculature of an AVF is hemodynamically mediated.[7] In this regard, examining the role of MCP-1 in AVF failure in the uremic setting would be of interest, the matter which was investigated in the present study.

PATIENTS AND METHODS

The study was performed as a cross sectional descriptive study in the hemodialysis units of Suez Canal University and Ismailia general hospitals. The aim of the study was determining the role of MCP-1 in hemodialysis induced inflammation. In addition to its relationship to dyslipidemia and AVF failure among ESRD. Ninety patients were enrolled in the study (adult patients > 18 years who were maintained on HD for at least 3 months to be sure that the observed effect can be attributed to the status of hemodialysis). In order to avoid the confounding effects of co-morbid conditions and concomitant drug usage on cytokine production the

following patients were excluded: Patients with autoimmune diseases or malignancies and Patients receiving antibiotics, corticosteroids, or cytotoxic drugs at the time of the study. Because there was unknown level for MCP-1 approved universally; 10 healthy persons –matched to the same age and gender of the patient group- were sampled to provide reference range for MCP-1.

Predialysis and postdialysis MCP-1 gene expression, CRP and lipid profile were done in addition to standard laboratory work up for ESRD patients. The standard current laboratory works up of the patients were obtained through reviewing their medical records and that includes: complete blood count, creatinine, urea, potassium, sodium, calcium, phosphorus, ALT, AST, and albumin levels in blood. All were determined by routine techniques using an automated analyzer (COBAS INTEGRA 400 Automated Chemistry Analyzer, used in SCU clinical pathology laboratory). Total RNA was extracted from the samples using SV Total RNA isolation system (Promega, Madison, WI, USA) and the extracted RNA was reverse transcribed into cDNA using RT-PCR kit (Stratagene, USA). After the amplification process, the DNA product was detected using agarose gel electrophoresis**.** Serum C-reactive protein (CRP) level was measured both predialysis and postdialysis session by nephelometry with a detection limit of 3.75 mg/l. Lipid profile including LDL, VLDL, HDL, Cholesterol and triglycerides using diagnostic kits provided from Spinreact, Spain, following the instructions of the manufacturers. Dyslipidemia was defined according to the guidelines of the National Cholesterol Education Program.

Ethical Consideration

Before the initiation of the study, informed consent was obtained from all individuals selected for the study. The aim and the value of the work were explained to them in a simplified manner. There was no harm being inflicted on them. On the contrary, all would have the benefits of follow-up and the results of the study. The study was approved by the ethics committee of the Faculty of Medicine, Suez Canal University.

Statistical Aspects

The data were coded and organized. The final study results were stated using the SPSS program version 20. Results were presented through tables and figures. The Student *t* test, correlation coefficient, and Chi-square tests were used to evaluate the results. Chi-square test was used for qualitative variables, while independent *t* test was used for quantitative variables. Correlation analysis was performed using Pearson's test. Statistical significance was considered at *P*-value <0.05.

RESULTS

Ninety patients were enrolled in the study. The age of patients ranged from 18 to 69 years with a mean value of 46.35 years, 63.33 % of them were male. Nearly half of patients had ESRD of uncertain etiology representing 48.90 % (**Figure 1**). The mean duration of dialysis was 5.41 years and **Figure 2** shows that the majority of them were maintained on HD for ≥6 – < 9 years accounting for 42.22 % of patients.

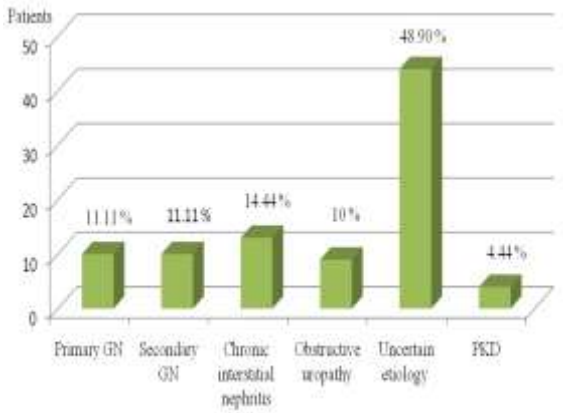

Figure 1. Distribution of patients according to their primary renal disease.

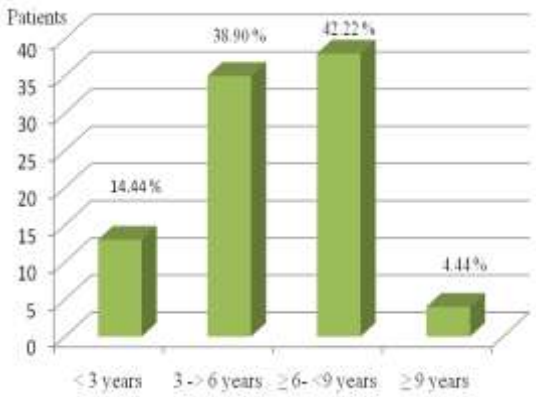

Figure 2. Distribution of patients according to their dialysis duration.

The study showed that the 25.56 % of patients experienced AVF failure at least once (**Figure 3**). Cholesterol and LDL levels (expressed in mg/dL) were significantly higher in patients who had experienced AVF failure than in patients with single functioning AVF (**Table 1**).

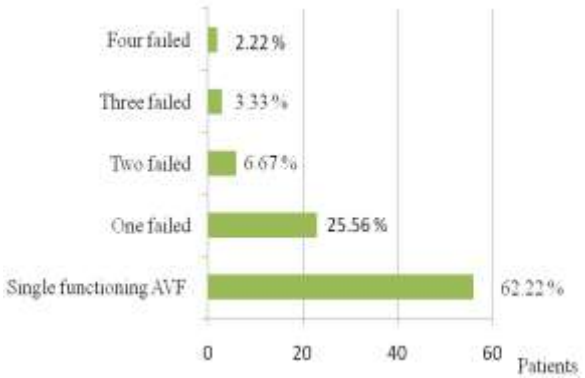

Figure 3. Distribution of patients according to the AVF status.

Table 1. Distribution of patients according to their lipid profile and incidence of AVF failure.

Parameter (Mean ± SD)	ESRD		*P* value
	AVF failure	Functioning AVF	
LDL mg/dL	102.35 ± 39.68	123.18 ± 45.42	0.02*
HDL mg/dL	30.43 ± 7.07	30.19 ± 6.63	0.8
Cholesterol mg/dL	171.08 ± 38.78	192.13 ± 57.16	0.05*
TG mg/dL	168.56 ± 93.34	219.28 ± 135.36	0.20

ESRD = end stage renal disease , AVF= arteriovenous fistula , LDL= low density lipoprotein , HDL = high density lipoprotein , TG = triglycerides , *= significant.

Statistic analysis for the inflammatory markers revealed that predialysis MCP-1, postdialysis MCP-1 and predialysis CRP levels are significantly higher in patients who had experienced AVF failure than in patients with single functioning AVF (**Table 2**).

Meanwhile logistic regression analysis for risk factors for AVF failure which revealed that smoking , prolonged dialysis duration and high predialysis MCP-1 level were significantly elevated in the studied patient group (**Table 3**).

Table 2. Distribution of patients according to their inflammatory markers and incidence of AVF failure.

Parameter (Mean ± SD)	ESRD (n=90)		*P* value
	Functioning AVF	Failed AVF	
MCP-1 gene expression pre- dialysis	3.24 ± 1.59	3.97 ± 1.77	0.02*
MCP-1 gene expression post- dialysis	12.05 ± 2.75	12.58 ± 3.23	0.04*
CRP pre-dialysis	8.25 ± 6.05	12.22 ± 9.08	0.05*
CRP post-dialysis	19.47 ± 6.73	22.98 ± 8.56	0.4

ESRD = end stage renal disease . AVF= arteriovenous fistula , MCP-1= Monocyte Chemoattractant Protien-1, CRP =C-Reative Protien , *= significant.

Table 3. Logistic regression analysis of risk factors for AVF failure in patients` group.

Parameter	AVF failure	
	Wald	*P* value
Age	1.13	0.28
Gender	1.94	0.16
Smoking	5.23	0.02*
Dialysis duration	7.76	0.005*
CRP pre-dialysis	0.004	0.95
CRP post-dialysis	0.42	0.52
MCP-1 gene expression pre-dialysis	7.52	0.006*
MCP-1 gene expression post-dialysis	2.48	0.11
LDL	0.79	0.37
HDL	1.96	0.19
Cholesterol	0.90	0.34
TG	0.002	0.96

Protien-1, CRP =C-Reactive Protein, *= significant

DISCUSSION

Up-and-coming evidences suggest that inflammation is concerned in the pathogenesis of cardiovascular diseases and MCP-1 has a central role in atherogenesis. The current study was performed to determine whether MCP-1 can be used as a marker for dialysis induced inflammation and AVF failure among ESRD patients.

The present study showed that both predialysis and postdialysis MCP-1 gene expression was significantly higher in patients who had experienced AVF failure than in patients with single functioning AVF. The previous finding was demonstrated earlier in one study on rodent AVF model where up-regulation of MCP-1 in the venous vasculature was found to be associated with dysfunction and failure of an AVF.[5]

In patients on maintenance hemodialysis, plasma levels of MCP-1, and other cytokines as IL-6 and plasminogen activator inhibitor-1, were demonstrated by Papayianni and colleagues[3] in 2002 to be risk factors for dysfunction of hemodialysis AVF. Furthermore, certain polymorphisms in the MCP-1 gene that lead to higher plasma levels of MCP-1 seem to be risk factors for cardiovascular disease in general.[8] Unfortunately there is paucity of human studies that investigate MCP-1 relation to AVF dysfunction specifically.

The present study showed that cholesterol and LDL levels were significantly higher in patients who had experienced AVF failure than in patients with single functioning AVF. Thus may be explained by the fact; AVF endothelium is affected by dyslipidemia, as any endothelium lining elsewhere in the vascular tree; mainly by the injurious effect of oxLDL. But logistic regression analysis failed to identify any type of dyslipidemia as a risk factor for AVF failure probably because CKD patients in general has low cholesterol levels and moderate LDL elevation when compared to general population with atherosclerosis and normal kidney function.

In a confirmatory manner to the previous finding, statin therapy failed to influence the occurrence of AVF failure as demonstrated by the study of Bahadi and colleague[9] in 2012 which included 115 patients with ESRD who underwent creation of 138 native AVFs. However, this was a retrospective observational study and only a randomized controlled interventional study would allow firm conclusions which are difficult to perform in ESRD population in which treatment protocols vary widely.

Also, the present study revealed that smoking and prolonged dialysis duration are a risk factors for AVF failure in contradiction to the old study done in University of Alabama at Birmingham dialysis patients during a two-year period which showed that smoking is not a risk factor for AVF failure.[10] This may be explained by the high prevalence of smokers in the

present study as 22.22 % were current smokers and 15.56 % were ex-smokers.

Such demonstration had been confirmed in experiments with mice rendered genetically deficient in MCP-1 or its key target receptor (CCR2) where there occurrence of atherosclerotic lesions were diminished significantly.[2,11] Moreover, even with hyperlipidemia, the knockout of the MCP-1 gene or its receptor CCR2 and anti-MCP-1 gene therapy had been shown to cause a significantly reduced progression of atherosclerosis in murine models with dietary-induced hyperlipidemia.[12,13]

CONCLUSION

Predialysis MCP-1 , postdialysis MCP-1 and predialysis CRP levels are significantly higher in patients who had experienced arteriovenous fistula failure. MCP-1 can be used as a novel marker for dialysis induced inflammation and AVF failure.

ACKNOWLEDGEMENT

The authors acknowledge the imperative contributions of many individuals to this study, Medical and nursing staff members in the hemodialysis unit, clinical pathology and internal medicine departments for their scientific technical support.

Source of Support: *Nil,*
Conflict of Interest: *Nil.*

REFERENCES

1. Simon A and Chironi G. The relationship between carotid intima-media thickness and coronary atherosclerosis revisited. European Heart Journal., 2007; 28(17): 2049–2050.
2. Niu J and Kolattukudy PE. Role of MCP-1 in cardiovascular disease: molecular mechanisms and clinical implications. Clinical Science., 2009; 117: 95–109.
3. Papayianni A, Alexopoulos E, Giamalis P, et al. Circulating levels of ICAM-1, VCAM-1, and MCP-1 are increased in haemodialysis patients: Association with inflammation, dyslipidaemia, and vascular events. Nephrol Dial Transplant., 2002; 17: 435–441.
4. Akahoshi T, Kobayashi N, Hosaka S, et al. In vivo induction of monocyte chemotactic and activating factor in patients with chronic renal failure. Nephrol Dial Transplant., 1995; 10: 2244–2249.
5. Juncos JP, Grande JP, Kang L, et al. MCP-1 Contributes to Arteriovenous Fistula Failure. J Am Soc Nephrol., 2011; 22: 43–48.
6. Deshmane SL, Kremlev S, Amini S, et al. Monocyte Chemoattractant Protein-1 (MCP-1): An Overview. J Interferon Cytokine Res., 2009; 29(6): 313–326.
7. Gruden G, Setti G, Hayward A, et al. Mechanical stretch induces monocyte chemoattractant activity via an NF-kappa B-dependent monocyte chemoattractant protein-1-mediated pathway in human mesangial cells: Inhibition by rosiglitazone. J Am Soc Nephrol., 2005; 16: 688– 696.
8. Buraczynska M, Bednarek-Skublewska A, Buraczynska K, et al. Monocyte chemoattractant protein-1 (MCP-1) gene polymorphism as a potential risk factor for cardiovascular disease in hemodialyzed patients. Cytokine., 2008; 44: 361–365.
9. Bahadi A, Hamzi MA, Farouki MR, et al. Predictors of early vascular-access failure in patients on hemodialysis. Saudi Journal of Kidney Diseases and Transplantation., 2012; 23(1): 83-87.
10. Miller PE , Tolwani A, Luscy CP ,et al. Predictors of adequacy of arteriovenous fistulas in hemodialysis patients. *Kidney International.*, 1999; 56: 275–280.
11. Schmidt AM and Stern DM. Chemokines on the Rise MCP-1 and Restenosis. Arterioscler Thromb Vasc Biol., 2001; 21: 297-299.
12. Schepers A, Eefting D, Bonta PI, Grimbergen JM, de Vries MR, van Weel V, et al . Anti-MCP-1 gene therapy inhibits vascular smooth muscle cells proliferation and attenuates vein graft thickening both in vitro and in vivo. Arterioscler Thromb Vasc Biol., 2006 Sep; 26(9): 2063-9.
13. Rajabi-Jaghargh E, Banerjee RK., Combined functional and anatomical diagnostic endpoints for assessing arteriovenous fistula dysfunction. World J Nephrol., 2015 Feb 6; 4(1): 6-18.