British Journal of Medicine & Medical Research
12(9): 1-8, 2016, Article no.BJMMR.22852
ISSN: 2231-0614, NLM ID: 101570965

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Monocyte Chemoattractant Protien-1 (MCP-1) and Atherosclerosis in End Stage Renal Disease Patients

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Authors' contributions

This work was carried out in collaboration between all authors. Author GAT designed the study and wrote the protocol. Authors FAK and SAO wrote the first draft of the manuscript. Author MMK managed the literature searches, conducted the practical study and performed all statistical analysis for the data. Author HS provided editing final form and publication process. All authors managed, collected data, performed the clinical and laboratory process, read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/22852
Editor(s):
(1) Toru Watanabe, Department of Pediatrics, Niigata City General Hospital, Japan.
Reviewers:
(1) Mario Ciampolini, University of Firenze, Italy.
(2) Sharon R. Inman, Ohio University College of Osteopathic Medicine, USA.
Complete Peer review History: http://sciencedomain.org/review-history/12470

Original Research Article

Received 31st October 2015
Accepted 16th November 2015
Published 27th November 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 to determine the role of MCP-1 in hemodialysis (HD) induced inflammation, dyslipidemia and atherosclerosis among end stage renal disease (ESRD) patients.
Methods: Ninety HD patients were enrolled in the study. Pre-dialysis and post-dialysis MCP-1 gene expression, C-reactive protein (CRP), lipid profile and Carotid duplex for the assessment of the presence of plaque, stenosis and the carotid intima/media thickness (IMT) were done in addition to standard laboratory work up for ESRD patients. Twenty healthy individuals were considered as a control group.
Results: The patients` mean age was 46.35 years, 63.33% of them were males. The most common dyslipidemia type was low serum HDL (87.78%) followed by hypertriglyceridemia. Pre-

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dialysis and post-dialysis values of MCP-1 gene expression and CRP plasma levels were significantly up-regulated during the HD session (P<0.001). When were compared to controls; both pre-dialysis and post-dialysis MCP-1 gene expressions were significantly higher in patients` group (P=0.004, P=0.0001). 42.2% of patients had carotid plaques, 11.1% had carotid stenosis and 62.2% had thick IMT. LDL, triglycerides and cholesterol levels were significantly higher in the affected carotid patient subgroup than the normal carotid subgroups. MCP-1 gene expression both pre-dialysis and post-dialysis were significantly higher in patients who had carotid plaques when compared to patient subgroup without plaques while MCP-1 gene expression was not significantly changed by dialysis in patient subgroups that had either thick carotid IMT or carotid stenosis.

Conclusion: The most common dyslipidemia types among current studied Egyptian ESRD patients are low HDL and hypertriglyceridemia which are found to be related significantly to the development of atherosclerosis in ESRD. CRP was higher in post-dialysis patients than the normal controls, but it failed to show any significant association with the observed carotid lesions. MCP-1 was significantly up-regulated during hemodialysis and it was associated with the occurrence of carotid atherosclerotic plaques.

Keywords: MCP-1; atherosclerosis; ESRD; CRP.

ABBREVIATIONS

End stage renal disease (ESRD); Hemodialysis (HD); Chronic kidney disease (CKD); Monocyte chemoattractant protein-1 (MCP-1); Cardiovascular disease (CVD); C- reactive protein (CRP); Intima/Media Thickness (IMT).

1. INTRODUCTION

It is well documented that cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with chronic kidney disease (CKD). Although some patients with CKD will ultimately develop end stage renal disease (ESRD), most of them will die of CVD before dialysis becomes necessary [1]. Nevertheless, when comparing mortality rate in dialysis patients with the general population, it is 30 times higher in dialysis patients [2].

According to Attman and Alaupovic [3], the atherogenic potential of dyslipidemia in CKD may depend more on the apolipoprotein than on lipid abnormalities and may not always be recognized by measurement of plasma lipids alone. An additional caveat is that, in many dialysis patients, CVD is caused or accentuated by other risk factors, such as volume overload, intima/media calcification and dysrhythmias, and may not necessarily be related to atherosclerosis. Furthermore, dyslipidemia in hemodialysis patients is characterized by hypertriglyceridemia, low serum HDL concentration, and usually normal levels of total and LDL cholesterol similar to the non-dialysis population with CKD [4]. However, it has been observed that additional factors like repeated use of heparin or type of membranes used in hemodialysis (HD) may affect lipid metabolism in these patients [5]. In the majority of published studies, peritoneal dialysis patients had more atherogenic lipid profile than those on hemodialysis [6].

Monocyte Chemoattractant Protein-1 (MCP-1) is a Chemotactic Cytokine produced by endothelial cells after exposure to cytokines (IL-1b, TNF-a) and oxidized lipoproteins. It plays an important role in the migration and activation of monocytes and T cells and moreover, regulates the proliferation of vascular smooth muscle cells [7]. Vascular insults can lead to endothelial dysfunction that causes increased leakage of LDL from the vessel lumen into the vessel walls that in addition to more secretion of MCP-1 from endothelial and smooth muscle cells [8].

Knockout of the MCP-1 gene or its receptor CCR2 and anti-MCP-1 gene therapy have been shown to cause a significantly reduced progression of atherosclerosis in murine models with dietary-induced hyperlipidemia [9]. In a rabbit model, inhibition of MCP-1 action by administration of a mutant MCP-1 inhibited plaque inflammation, reversed plaque progression and prevented rupture of vulnerable plaques, but did not affect lipid profile [10]. In support of the role of MCP-1 in atherosclerosis, overexpression of MCP-1 in the arterial wall of hypercholesterolemic rabbits produced increased macrophage infiltration and accelerated atherosclerosis [11].

Some studies suggested that, the serum level of MCP-1 is increased in ESRD patients as a result from either inadequate clearance or enhanced synthesis and release [12]. Moreover, the HD session resulted in a significant increase of the MCP-1 molecule level but the exact mechanisms responsible for this alteration are yet to be fully elucidated. The influence of the HD membranes on their secretion had been suggested. Both modified cellulose and polysulfone membranes resulted in a significant and comparable increase of these molecule levels after correcting for hemoconcentration as suggested by the old study of Akahoshi et al. [13].

Likewise, due to lack of the studies that link MCP-1 to dyslipidemia and atherosclerosis in this particular population and shortage of evidence in humans as most of the previous works were in marine animals; it is advocated to study that in humans. In this aspect, the present study was designed to determine the role of MCP-1 in hemodialysis-induced inflammation and its relationship to dyslipidemia and atherosclerosis among ESRD patients who are maintained on regular HD.

2. PATIENTS AND METHODS

The current study was performed as a cross-sectional descriptive study. Ninety HD patients – randomly selected from the hemodialysis units of Suez Canal University and Ismailia general hospitals- were enrolled in the study. All were 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 in cytokine production, the following patients were excluded: Patients with autoimmune diseases or malignancies and those receiving antibiotics, corticosteroids, or cytotoxic drugs at the time of the study. Because there was an unknown level for MCP-1 approved universally; Twenty healthy persons, matched to the same age and gender of the patients, were sampled to provide a reference range for it and considered as a control group.

Pre-dialysis and post-dialysis MCP-1 gene expression, CRP, lipid profile and Carotid duplex were done in addition to standard laboratory work up for ESRD patients. The standard current laboratory workup of the patients was obtained through reviewing their medical records and that includes: complete blood count, creatinine, urea, potassium, sodium, calcium, phosphorus, ALT, AST, albumin, parathyroid hormone and ferritin 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 an RT - PCR kit (Stratagene, USA). After the amplification process, the DNA product was detected using agarose gel electrophoresis**.**

CRP levels were measured both pre-dialysis and post-dialysis 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 and dyslipidemia was defined according to the guidelines of the National Cholesterol Education Program [14] .

A carotid artery duplex was done for all patients to demonstrate any atherosclerotic process and the Intima/Media Thickness of the carotid artery was used as an index for that (normal carotid IMT < 0.8 mm).

2.1 Ethical Consideration

Before the initiation of the study, informed consent was obtained from all individuals chosen 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.

2.2 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. The Student *t* test, correlation coefficient, and Chi-square tests were used to evaluate the results. The chi - square test was used for qualitative variables while the 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.

3. RESULTS

The study was performed upon 90 patients. Age of the patients ranged from 18 to 69 years with a

mean value of 46.35 years, 63.33 % of them were male. The mean duration of dialysis was 5.41 years. Their biochemical data are shown in Table 1. The most dyslipidemia types encountered in the studied group, were low serum HDL (87.78%) followed by hypertriglyceridemia and nearly in half of the patients LDL serum level was optimal accounting 46.66% of them.

MCP-1 gene expression was significantly up-regulated during an HD session with a mean blood level of 3.66 pre-dialysis compared to a mean blood level of 12.37 post-dialysis. It is also observed that, both pre-dialysis and post-dialysis CRP plasma levels were significantly changed with a mean of 10.59 and 21.54 respectively (Table 2).

Both pre-dialysis and post-dialysis MCP-1 gene expression and post dialysis CRP plasma levels were significantly higher in the patients` group when compared to control group. On the other hand, CRP plasma levels showed no significant elevation in pre-dialysis values compared to control group (Table 3).

Carotid duplex showed that 42.22% of patients had carotid plaques, 11.11% had carotid stenosis and 62.22% had thick IMT, which represented a significant proportion of patients except for those with carotid plaques. MCP-1 gene expressions both pre-dialysis and post-dialysis were significantly higher in patients who had carotid plaques when compared to patient subgroup without plaques while MCP-1 gene expression was not significantly changed by dialysis in patient subgroups who either had thick carotid IMT or carotid stenosis. In the meantime, CRP plasma levels were insignificantly changed both pre-dialysis and post-dialysis for all subgroups except the patient subgroup with thick IMT where pre-dialysis plasma CRP levels showed a weak significant change (Table 4).

Logistic regression analysis of various risk factors for developing carotid artery affection in the patients` group; age was the most constant and highly significant factor in all subgroups followed by dialysis duration that was significant in both carotid plaque and thick IMT subgroups. Regarding inflammatory markers, only post-dialysis CRP plasma levels were significantly associated with the development of carotid stenosis while both pre-dialysis and post-dialysis MCP-1 gene expressions were significantly associated with the development of carotid plaques. Strikingly, all plasma lipid types were not significantly associated with the carotid affection of any subgroup except for carotid plaque subgroup where serum LDL was found to be a significant risk factor (Table 5).

Table 1. Biochemical and nutritional parameters of the patients

Parameter	Mean ±SD
Hemoglobin (g/dl)	9.55±1.07
Sodium (mEqu/l)	141.94 ±3.53
Potassium (mEqu/l)	5.20±0.42
Calcium (mg/dl)	8.32±0.57
Phosphorus (mg/dl)	5.31±1.18
Creatinine (mg/dl)	8.62±1.61
Albumin (g/dl)	4.43±0.74
PTH (pg/dl)	555.76±337.02
Ferritin (ng/dl)	556.66±357.78
LDL (mg/dl)	114.62±44.19
HDL (mg/dl)	30.29±6.78
Cholesterol (mg/dl)	183.48±51.24
Triglycerides (mg/dl)	205.83±120.38

PTH= parathyroid hormone, LDL= low density lipoprotein, HDL = high-density lipoprotein,

Table 2. Distribution of inflammatory marker of the patients

Parameter	ESRD		*P* value
	Pre-dialysis	Post-dialysis	
MCP-1 gene expression	3.66±1.73	12.37±3.03	0.0001*
CRP(mg/L)	10.59±8.17	21.54±8.01	0.0001*

*MCP-1= Monocyte Chemoattractant Protien-1, CRP =C-Reactive Protein, * = significant*

Table 3. Distribution of inflammatory markers of patients and control groups

Parameter	N(90)	N(20)	*P* value
	Pre-dialysis	Control	
MCP-1 gene expression	3.66±1.73	1.09±0.16	0.004*
CRP (mg/L)	10.59±8.17	3.29±1.46	0.07
	Post-dialysis	Control	
MCP-1 gene expression	12.37±3.03	1.09±0.16	0.0001*
CRP (mg/L)	21.54±8.01	3.29±1.46	0.0001*

*MCP-1= Monocyte Chemoattractant Protien-1; CRP =C-Reactive Protein, * = significant*

Table 4. Distribution of patients according to their inflammatory markers and carotid ultrasonographic data

Parameter (Mean ± SD)	ESRD		*P* value
	Carotid plaques	**No plaques**	
MCP-1 gene expression pre- dialysis	3.07±1.35	4.08±1.86	0.007
MCP-1 gene expression post- dialysis	13.13±2.64	11.81±3.21	0.004*
CRP pre-dialysis (mg/L)	10.37±9.25	10.75±7.38	0.82
CRP post-dialysis (mg/L)	21.36±9.33	21.67±6.99	0.85
	Thickened IMT	**Normal IMT**	***P* value**
MCP-1 gene expression pre- dialysis	3.39±1.57	4.12±1.89	0.29
MCP-1 gene expression post- dialysis	12.27±2.98	12.53±3.15	0.54
CRP pre-dialysis (mg/L)	11.29±9.16	9.43±6.17	0.05*
CRP post-dialysis (mg/L)	21.94±8.75	20.87 ±6.69	0.6
	Stenosed	**Non-stenosed**	***P* value**
MCP-1 gene expression pre- dialysis	3.8±1.34	3.73±1.76	0.34
MCP-1 gene expression post- dialysis	13.25±2.49	12.25±3.9	0.33
CRP pre-dialysis (mg/L)	11.19±7.53	10.51±8.29	0.80
CRP post-dialysis (mg/L)	25.61±8.97	21.03±7.79	0.79

ESRD = end stage renal disease, IMT = intimal medial thickness, MCP-1= Monocyte Chemoattractant Protien-1, CRP =C-Reactive Protein

Table 5. Logistic regression analysis of risk factors for carotid affection in patients` group

Parameter	Carotid plaques		Thickened IMT		Carotid stenosis	
	Wald	***P* value**	**Wald**	***P***	**Wald**	***P* value**
Age	8.62	0.003*	9.81	0.001*	6.05	0.01*
Gender	2.02	0.1	1.75	0.18	0.85	0.35
Smoking	0.51	0.47	0.11	0.73	0.77	0.37
Dialysis duration	6.46	0.01*	4.08	0.04*	0.04	0.83
CRP pre-dialysis	0.66	0.42	3.42	0.06	3.49	0.06
CRP post-dialysis	1.15	0.28	3.11	0.07	3.83	0.05*
MCP-1 gene expression pre-dialysis	9.46	0.002*	0.77	0.38	1.85	0.17
MCP-1 gene expression post-dialysis	8.53	0.003*	0.06	0.81	1.79	0.18
LDL	4.43	0.03*	0.004	0.94	0.70	0.40
HDL	1.18	0.28	0.50	0.43	0.40	0.52
Cholesterol	2.41	0.12	0.02	0.80	3.47	0.06
Triglycerides	1.19	0.27	1.42	0.23	1.92	0.16

*LDL= low density lipoprotein, HDL = high-density lipoprotein, IMT = intimal medial thickness, MCP-1= Monocyte Chemoattractant Protien-1, CRP =C-Reactive Protein *= significant*

4. DISCUSSION

The most common dyslipidemia types encountered in the current study, according to the ATP III were low serum HDL followed by hypertriglyceridemia. Comparing the results to another similar previous study, there is a difference. Prichard study, which was conducted upon US relatively elder dialysis patients had declared that hypertriglyceridemia is the most prevalent subtype followed by low HDL-C [15].

Logistic regression analysis of the lipid profile of the current patients did not yield significant association with the occurrence of carotid plaques except for LDL association. The existing results come into agreement with other previous studies by default et al. [16] and Shlipak et al. [17]. Both failed to find a definite significant correlation between dyslipidemia and CVD including atherosclerosis.

By demonstrating the representative current and previous data, we recognized that the findings on the association of dyslipidemia with cardiovascular events including atherosclerosis in patients with ESRD were not uniform. Obviously, the relation is confounded and the most potent cofounder apparently is micro-inflammation as reported in the early study of Pecoits‐Filho et al. [18]. By the way, it should be mentioned that lipid peroxidation has a strong

correlation to the process of atherosclerosis which is more evident in HD patients due to the micro-inflammatory status. In agreement with this hypothesis the Lobo et al.[19] found that levels of OX-LDL is higher in CKD and dialysis patients when compared to the general population and it is correlated significantly with CVD.

Regarding the MCP-1 gene expression, to our knowledge, there were no clinical trials done to evaluate either plasma MCP-1 levels or gene expression in ESRD patients experiencing atherosclerotic changes. The available data from studies done upon patients other than ESRD population demonstrated clearly that MCP-1 is correlated to atherosclerosis. For example, larger prospective human studies were done in 2004 by Rajat et al. [20] and in 2009 by Piemonti et al. [21]. Both studies showed a clear association between MCP-1 and several traditional cardiovascular risk factors such as age, hypercholesterolemia, hypertension, diabetes, and renal insufficiency and furthermore, MCP-1 can be used as a biomarker during the preclinical phase of atherosclerosis. Up to date in 2014, an experimental study done on mice; MCP-1 was found to be associated with carotid intima-media thickness, which reflects generalized atherosclerosis and is predictive of future vascular events [22].

On this aspect, the present study verified that, both pre-dialysis and post-dialysis levels of CRP and MCP-1 gene expressions were significantly higher than normal, indicating that a general state of micro-inflammation beyond doubt existed in the HD patients. Furthermore, MCP-1 gene expression was unregulated significantly in patients who had carotid plaques compared to patients without plaques. Neither CRP level nor MCP-1 gene expression showed definite significant alteration with hemodialysis in patients with carotid thick IMT and stenosis. This was confirmed on logistic regression analysis of the data which revealed that MCP-1 gene expressions were significantly associated with the occurrence of carotid plaques only, but a weak association was found between post-dialysis CRP levels and carotid stenosis. Such finding may indicate that MCP-1, as inflammatory cytokines, may be involved or even play a role in the progression of atherosclerosis.

What is the explanation of this raised MCP-1 expression in HD? Interestingly, one study demonstrated that exposure of peripheral blood monocytes to cuprophane membranes resulted in MCP-1 mRNA overexpression and the improvement of the ability of peripheral blood monocytes to secrete this cytokine [12]. This may partially explain the particularly increased MCP-1 levels in our studied HD patient population.

The current data are coincident with the results of a previous study assessed the carotid artery stiffness and its relationship to CRP and other cytokines like IL-6 and TNF-α in HD patients. Recorded current data had exposed that CRP was higher in post-dialysis patients than normal controls, but it failed to show any significant association with the observed carotid lesions. These results were in agreement with Ren H et al. [23] but were contradictory to the result of another cross-sectional studies that showed elevated CRP level as a surrogate marker for atherosclerotic vascular disease in HD patients [24]. In the same context, back to 1998; CREED (cardiovascular risk extended evaluation in dialysis) investigators provided evidence that CRP level is an independent predictor of atherosclerotic carotid plaques in 112 chronic HD patients. Their results were the triggers which suggested that, oxidative stress, inflammation and atherosclerosis might have an informal relationship [25]. Variations of the obtained results may be attributed to different medical and demographic aspects of the studied population.

In a demographic aspect, the present study showed that patients` age was the most constant risk factor for carotid artery affection in the form of thick IMT, plaque formation and stenosis followed by dialysis duration which was significantly associated with the occurrence of both carotid plaque and thick IMT subgroups. This result was in agreement with findings of Savage and colleagues [26] in 1998 who noted the correlation between age and carotid IMT in a study on 24 dialysis patients and a few years later in 2003, Kato et al. [27] in a larger study on 219 hemodialysis patients observed a similar significant correlation between IMT and age. More recently, in 2013 these findings were confirmed again by Rafieian-Kopaei et al. [28], However, they did not detect any association between the duration of HD and atherosclerosis. In the same context the old studies of Shoji et al. [29] and Hojs et al. [30] showed no relationship between IMT and duration of HD was established.

5. CONCLUSION

The most common dyslipidemia types among current studied Egyptian ESRD patients are low

HDL and hypertriglyceridemia which are found to be related significantly to the development of atherosclerosis in ESRD. CRP was higher in post-dialysis patients than normal controls, but it failed to show any significant association with the observed carotid lesions MCP-1 was significantly up-regulated during hemodialysis and it was associated with occurrence of carotid atherosclerotic plaques. MCP-1 is a promising biomarker that can be used as a marker for dialysis-induced inflammation and atherosclerosis. MCP-1 to be a potential therapeutic target; further prospective studies of this chemotactic cytokine are required.

ACKNOWLEDGEMENT

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

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/12470