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Study the Association between Dyslipidemia and CCL2 in Patients Undergoing Hemodialysis

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Abstract

Background: Chronic kidney disease (CKD) is becoming a major public health problem worldwide, with a high prevalence in developing countries. C-C Motif Chemokine Ligand 2 (CCL2), also known as monocyte chemotactic protein-1 (MCP-1) can be produced by a variety of cells, reaching increased levels in dyslipidemic patients.Aim: The present study was to identify the relation between dyslipidemia and CCL2 in patients undergoing hemodialysis.Subjects and methods: This case-control study was conducted on 80 subjects: 60 hemodialyzed patients who were recruited from the Nephrology Department and Renal Dialysis Unit at Benha University Hospital and 20 apparently healthy controls. All participants were subjected to full history taking, complete clinical examination, and laboratory investigations including lipid profile and CCL2 were measured. The association between CCL2 levels and dyslipidemia was investigated using linear regression, adjusted for classic and non-classical CVD risk factors.Results: A significant association was observed between CCL2 levels and dyslipidemia (P<0.001), even after adjustment for possible confounding variables, such as age and gender (P=0.001), as well as, predictor after adjustment with body mass index, diabetes mellitus, HD time, and urea (P<0.001). Conclusion: Our study suggests that CCL2 levels may contribute to the development of cardiovascular disease in HD patients by promoting dyslipidemia. Through a better understanding of this pathogenesis, new therapeutic targets could be discovered to reduce cardiovascular complications for these patients.

Keywords: Dyslipidemia; CCL2; Chronic kidney disease and Hemodialysis**.**

1. Introduction

Hemodialysis (HD) is linked to a higher risk of cardiovascular disease, such as a heart attack, stroke, or congestive heart failure **[1]**. In individuals with chronic kidney disease (CKD) in HD, the death rate from ischemic heart disease was 5–10 times greater than in the general population **[2]**. Cardiovascular disease (CVD) is recognized to be linked to a number of risk factors; including dyslipidemia, uremia, oxidative stress, endothelial dysfunction, diabetes, and an inflammatory state **[3].** Dylipidemia is characterised by changes in the concentration of one or more lipids/lipoproteins present in the blood [triglycerides (TG), total cholesterol (TC), high density lipoproteins (HDL), and low-density lipoproteins (LDL)] and is thought to be linked to the development of CVD **[1]**. Dyslipidemia causes endothelial dysfunction, which increases the permeability of the intima to plasma lipoproteins, favoring their retention in the subendothelial space. Retained LDL particles undergo oxidation. Oxidized LDL-c stimulates the endothelial cells expression of vascular adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), P and E-selection **[4]**. The attraction of monocytes and lymphocytes to the intima of the artery wall is mediated by adhesion molecules. Monocytes travel into the subendothelial region, where they differentiate into macrophages, which then collect oxidized LDL, triggered by chemotactic proteins such as C-C Motif Chemokine Ligand 2 (CCL2), also known as monocyte chemotactic protein-1(MCP-1) and interleukin-8 (IL-8) **[5]**. These macrophages engulf the oxidized LDL and become lipid-laden, giving them a foamy look and making fatty streaks possible **[6]**. Once activated, macrophages play a major role in the progression of atherosclerotic plaques by secreting cytokines [IL-1, tumor necrosis factor (TNF-), transforming growth factor-1(TGF-1)] that increase inflammation, smooth muscle cell proliferation and proteolytic enzymes that degrade collagen and other local tissue components **[7]**. A number of mesenchymal cells, including glomerular cells, can generate CCL2. The link between CCL2 levels and glomerular disease could be due to alterations associated with CKD as well as the glomerular lesion itself. In patients with glomerular disorders, there was a link between CCL2 levels in the urine and cholesterol and triglyceride levels. Renal impairment is known to be caused by an excess of cellular lipids [8, 9]. Therefore, this study aimed to identify the relation between dyslipidemia and CCL_2 in patients undergoing hemodialysis.

2. Subjects and methods

This case control study was conducted on 80 subjects who were recruited during the period from May 2021 to December 2021. The study was conducted in the Immunology Unit, Department of Clinical and Chemical Pathology, Faculty of Medicine, Benha University. Subjects were divided into two groups: **Group I (patient group):** It included 60 patients with chronic kidney disease (CKD) undergoing HD. Their mean age was

(51.3±12.2) years and they were 39 males (65%) and 21 females (35%) and **Group II (control group):** It included 20 apparently healthy control subjects. Their mean age was (52.3±10.9) years, and they were 11 males (55%) and 9 females (45%). Inclusion criteria: Patients age from 50 to 70 years old with minimum 6-month HD time. Their diagnosis was based on Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for chronic kidney disease which provided evidence based guidelines for all stages of chronic kidney diseases **[10]**. Exclusion criteria: According to the clinician who examined the subjects, none of them had liver diseases, tumors, systemic lupus erythematosus (SLE), coagulopathies, vasculitis, acute disease, history of renal transplantation, serum positive for HIV and pregnancy. Ethical consideration: Ethical permission for the study was obtained from all subjects after fully informed about all study procedures and their consent was obtained prior to enrollment in the study. This study was approved by the Ethical Committees of Benha Faculty of Medicine, Benha University.

Both groups were subjected to the following:

1. **Full history taking including:** age, sex, HD duration, primary cause of CKD, and presence of diabetes.
2. **Thorough physical and clinical examination including:**
3. body mass index (BMI): was calculated as weight in kilograms divided by the squared of height in meters (kg/m^2). Blood pressure was measured while the patients were in seated and relaxed position **[11].**

Laboratory measurement

Blood sampling

Five milliliters of venous blood sample were collected from subjects who were fasted for 12 hours under complete aseptic conditions. The samples were collected in plain tubes, allowed to be clot for 20 minutes at room temperature and centrifuged at 1300 rpm for 20 minutes. Serum was separated and used for measurement of creatinine, urea, lipid profile, fasting blood sugar (FBS), and CCL2. Serum was stored at -40^o C till analysis.

Routine laboratory investigations:

Clinical chemistry tests were done using Bio-system A15 auto-analyzer, Spain. Investigations include: FBS **[12],** creatinine **[13];** urea **[14]**; lipid profile including TC **[15]**, HDL-c **[16]**, triglycerides **[17],** to characterize the presence of dyslipidemias. Dyslipidemia was defined as TC ≥ 200 mg/dl, or TG ≥150 mg/dl, or LDL-C ≥ 130 mg/dl, or HDL-C < 40 mg/dl (for men) and HDL-C < 50 (for women) **[18]**.

While LDL-c was calculated using the following equation (The TG value was less than 400 mg/dl) **[19]**:

$$LDL = TC - HDL - \frac{Triglyceride}{5}$$

Creatinine clearance was calculated using the following equation [13]:

$$\text{Creatinine clearance} = \frac{U.V}{P}\ x\ \frac{1}{1440}$$

U, V, and P were the urine creatinine level (mg/dl), the urine volume in 24 hours, and the plasma.

Creatinine level respectively. A 24-hour urine collection was done by collecting midstream urine in a special container over a full 24-hour period. The container must be kept cool in the refrigerator until the urine is returned to the lab **[13]**.

Measurement of CCL2 levels

Using the enzyme-linked immunosorbent assay (ELISA), (Human Monocyte Chemotactic Protein 1 ELISA Kit (MCP1), Catalog No. RK00052, ABclonal Biotechnology Co., Ltd, Woburn, England. This assay employs the quantitative sandwich enzyme immunoassay technique. An antibody specific for human MCPI has been pre-coated onto a micro-plate. Standards and samples were pipetted into the wells and MCPI was bound by the immobilized antibody. A detection antibody specific for MCPI binded to the combination of capture antibody MCPI in sample then enzyme conjugate was added. Following incubation and wash steps, a substrate solution was added to the wells and color developed in proportion to the amount of MCPI bound in the initial step. The color development was stopped and the absorbance was measured. A standard curve was created by plotting the mean absorbance for each standard on the Y-axis against the concentration on the X-axis and draw a best fit curve through the points on a log/log graph [20].

3. Statistical analysis

The collected analyzed to a PC using Statistical package for Social Science (SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp, 2017.). Mean, Standard deviation (± SD) used for parametric numerical data, while used Median and range for non-parametric numerical data. Kolmogorov Smerinov test, Student T Test, ANOVA, Mann Whitney Test (U test), Kruskal-Wallis test, Chi-Square test and Fisher's exact test were used. Correlation analysis: To assess the strength of association between two quantitative variables. The ROC curve (receiver operating characteristic) provides a useful way to evaluate the sensitivity and specificity for quantitative diagnostic measures that categorize cases into one of two groups. The optimum cut off point was defined as that which maximized the AUC value.

AUC is that a test with an area greater than 0.9 has high accuracy, while 0.7–0.9 indicates moderate accuracy, 0.5–0.7, low accuracy and 0.5 a chance result. Odds ratio and 95% confidence interval were calculated. P value is considered significant if <0.05 at confidence interval 95%.

4. Results

Hemodialyzed patients were significantly associated with lower BMI, and higher SBP when compared to the control group (p=0.001, 0.024 respectively). In contrast, DBP didn't differ significantly between both groups.

Regarding laboratory findings; hemodialyzed cases had significantly higher TC, TG, LDL-c, FBS, creatinine, urea, and significantly lower creatinine clearance when compared to the control group (p<0.001, =0.017, <0.001, =0.001, <0.001, <0.001, <0.001 respectively) **Table (1)**.

In hemodialyzed cases, 76.7% are dyslipidemic and 23.3% are non-dyslipidemic; while in the control group, 25% are dyslipidemic and 75% are non-dyslipidemic. A higher proportion of dyslipidemia was significantly associated with hemodialyzed cases when compared to the control group (p<0.001) **Fig (1)**. hemodialyzed cases had significantly higher CCL2 when compared to the control group (mean=1491.1 versus 950.4, p<0.001) **Fig (2)**.

Regarding dyslipidemic subjects, hemodialyzed patients had higher CCL2 when compared to the control group (mean CCL2=1666.1 pg/ml versus 1170.2 pg/ml, p<0.001). In non-dyslipidemic subjects, hemodialyzed patients had higher CCL2 when compared to the control group (mean CCL2=915.9 pg/ml vs 877.1 pg/ml, p=0.005). Regarding hemodialyzed cases, dyslipidemic cases had higher CCL2 when compared to non-dyslipidemic cases (mean CCL2=1666.1 pg/ml versus 915.9 pg/ml, p=0.008). Dyslipidemic cases in the control group had non-significantly higher CCL2 when compared to non-dyslipidemic cases (mean CCL2=1170.2 pg/ml versus 877.1pg/ml, p>0.05) **Table (2)**.

ROC curve of CCL2 level was conducted for discrimination between hemodialysis cases and the control group. CCL2 showed moderate accuracy AUC (AUC=0.836). At the best cut-off value of 1060 (pg/ml), sensitivity was 80%, specificity was 85%, PPV was 94.1%, NPV was 58.6% and accuracy was 81.3% **Table (3)**.

ROC curve of CCL2 level was conducted for discrimination between dyslipidemia and non-dyslipidemia among all studied subjects. CCL2 showed high accuracy AUC (AUC=0.972). At the best cut-off value of 1268 (pg/ml), sensitivity was 92.2%, specificity was 86.2%, PPV was 92.2%, NPV was 86.3% and accuracy was 90% **Table (3)**.

In addition, the ROC curve of CCL2 level was conducted for discrimination between dyslipidemia and non-dyslipidemia among hemodialyzed patients. CCL2 showed high accuracy, AUC (AUC=0.968). At the best cut-off value of 1278 (pg/ml), sensitivity was 87%, specificity was 100%, PPV was 100%, NPV was 70.1% and accuracy was 90%. CCL2 was higher than 1278 pg/ml, we can predict dyslipidemia in CKD cases undergoing hemodialysis with a sensitivity of 87% and perfect specificity **Table (3)**.

CCL2 in hemodialyzed patients showed significant positive correlations with urea, TC, and LDL-c (p<0.001, =0.001, <0.001 respectively). Otherwise, no significant correlations were found between CCL2 and other parameters (p>0.05 for each) **Table (4)**.

CCL2 was considered a risk predictor in the crude model (p<0.001, OR>1). Moreover, in adjusted models, CCL2 was considered a risk predictor after adjustment with age and gender (p=0.001, OR>1), as well as, a predictor after adjustment with BMI, DM, hemodialysis time, and urea (p<0.001, OR>1). So, CCL2 was considered an independent risk predictor for dyslipidemia occurrence in hemodialyzed cases even after adjustment with other confounders **Table (5)**.

Table (1): Comparison of laboratory data among studied groups.

		Control		Hemodialyzed patients N=60		p
		N=20				
Cholesterol (mg/dl)	Mean±SD	144.1	27.7	194.3	53.2	<0.001
TG (mg/dl)	Mean±SD	89.0	5.5	113.0	33.5	0.017
HDL-c (mg/dl)	Mean±SD	57.3	7.6	61.0	16.5	0.338
LDL-c (mg/dl)	Mean±SD	69.0	19.6	109.6	32.4	<0.001
FBG (mg/dl)	Mean±SD	89.4	9.5	141.4	47.7	0.001
Creatinine (mg/dl)	Mean±SD	1.1	0.1	9.9	2.9	<0.001
Urea (mg/dl)	Mean±SD	30.4	6.3	153.9	46.2	<0.001
Creatinine Clearance (ml/min)	median, range	102.5	85-117	7.2	2.1-46.6	<0.001

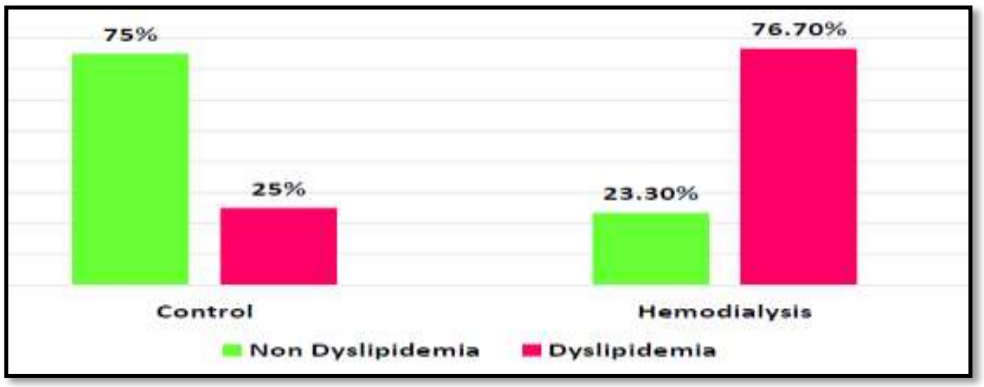

Fig (1): Dyslipidemia among studied groups.

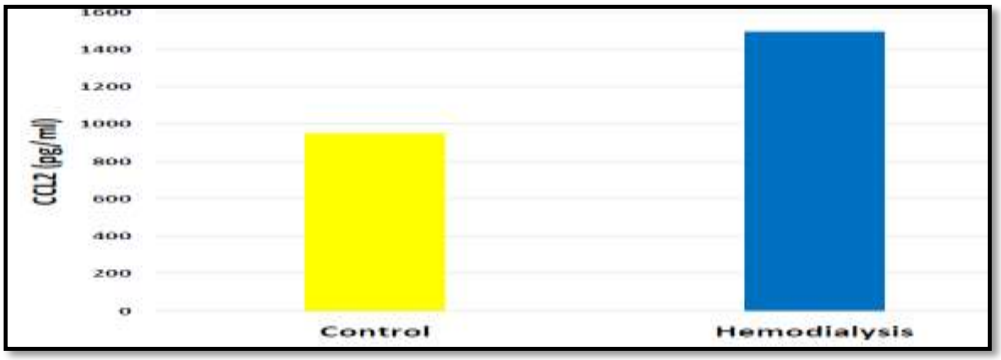

Fig (2): Serum CCL2 level among cases and control group**.**

Table (2): Comparison of CCL2 level among studied groups stratified by dyslipidemia.

	Control		**hemodialyzed patients**		***p*1**
			N=60		
	N=20				
	mean	**SD**	**mean**	**SD**	
Non Dyslipidemia (pg/ml)	**877.1**	**174.0**	**915.9**	**229.1**	**0.005**
Dyslipidemia (pg/ml)	**1170.2**	**198.0**	**1666.1**	**536.0**	**<0.001**
p2	**0.610**		**0.008**		

P1,comparison between CKD cases and controls.
P2, comparison between nondyslipidemia and dyslipidemia.

Table (3): Validity of serum CCL2 level for discrimination between hemodialyzed cases and control group (ROC1), dyslipidemia and non-dyslipidemia among all studied subjects (ROC2), and dyslipidemia and non-dyslipidemia among hemodialyzed cases (ROC3).

	(ROC1)	**(ROC2)**	**(ROC3)**
	Serum CCL2 (pg/ml)	**Serum CCL2 (pg/ml)**	**Serum CCL2 (pg/ml)**
AUC	**0.836**	0.972	0.968
Cutoff (pg/ml)	**1060**	1268	1278
Sensitivity (%)	**80**	92.2	87
Specificity (%)	**85**	86.2	100
PPV (%)	**94.1**	92.2	100
NPV (%)	**58.6**	86.3	70.1
Accuracy (%)	**81.3**	90	90

AUC, area under curve; ROC, receiver operating curve; PPV, positive predictive value; NPV, negative predictive value.

Table (4): Correlations of serum CCL2 level with other parameters among studied hemodialyzed patients**.**

	Hemodialyzed patients	
	CCL2 (pg/ml)	
	r	p
Age (years)	0.194	0.138
HD duration	0.002	0.989
SBP (mmHg)	0.016	0.904
DBP (mmHg)	-0.138	0.292
BMI (kg/m^2)	0.039	0.770
Creatinine (mg/dl)	0.161	0.022
Urea (mg/dl)	0.517	<0.001
F.B.S (mg/dl)	-0.020	0.880
Creatinine clearance (ml/min)	0.111	0.399
TC (mg/dl)	0.410	0.001
TG (mg/dl)	0.212	0.103
HDL-c (mg/dl)	0.226	0.082
LDL-c (mg/dl)	0.451	<0.001

r, correlation coefficient

Table (5): Regression analysis for prediction of dyslipidemia in hemodialyzed cases.

	p	OR	95%CI	
CCL2*	<0.001	1.005	1.002	1.011
CCL2#	0.001	1.006	1.002	1.010
CCL2$	<0.001	1.006	1.003	1.009

OR, odds ratio; CI, confidence interval. Logistic regression test was used.
*Unavailable analysis (crude model);
#Adjusted for age and sex; $ adjusted for BMI, DM, hemodialysis time, and urea.

5. Discussion

Dialysis is a form of renal replacement therapy. CKD is defined by at least 3 months of impaired kidney function or albuminuria **[21].**

CCL2 upregulation has been receiving particular interest in its roles in inflammation and can be produced by a variety of mesenchymal cells, including glomerular cells. The association between CCL2 levels and glomerular disease may be related to changes associated with CKD as well as with repair in kidney disease progression **[22].**

In the present study, there is a statistically significant increase in SBP and decrease in BMI in hemodialyzed patients when compared to the control group (p=0.001, 0.024 respectively), while DBP did not differ significantly between both groups. It was revealed that higher systolic blood pressure among males was associated with more renal function decline than in women **[23]**. Another study revealed that factors independently associated with CKD were age, female gender, BMI, high waist circumference, hypertension, and dyslipidemia **[24]**.

As regards the laboratory data among the studied groups in this research, hemodialyzed patients had significantly higher TC, TG, LDL-c, FBS, creatinine, urea, and significantly lower creatinine clearance when compared to the control group (p<0.001,=0.017, <0.001, =0.001, <0.001, <0.001, <0.001 respectively), and another report, revealed that LDL-c and TG were significantly higher in the hemodialyzed patients while HDL-c was significantly lower in the hemodialyzed patients when compared to control group **[25].**

It was reported that there was an increase in TC, LDL-c, VLDL, and TG and a decrease in HDL-c in all hemodialyzed patients compared to healthy controls **[26].** Either lower or higher TC, higher LDL-cholesterol, and higher non-HDL cholesterol were risk factors for renal replacement therapy (RRT) in stage 3–5 CKD patients. Higher TC was also significantly associated with rapid renal progression **[27].**

According to this study, a higher proportion of dyslipidemia was significantly associated with hemodialyzed patients when compared to the control group (76.7% versus 25%), and this agreed with another study that showed, the overall prevalence of dyslipidemia in the hemodialyzed patients was 60% and was commoner in those who were 45 years and above **[25]**. In addition, it was found that dyslipidemia was present in 45% of the study cases with CKD and 22.5% in the control group **[28]**.

In this study, hemodialyzed patients had significantly higher CCL2 when compared to the control group ($p<0.001$) and this agreed with the previous studies which found a significant association of CCL2 levels with CKD in the pre-hemodialysis stage **[29, 30].**

It was found that CCL2 serum levels were significantly higher in patients with diabetic nephropathy than those without diabetic nephropathy. These results showed that CCL2 serum can be considered a diagnostic biomarker for the detection of nephropathy in the pre-hemodialysis stage and will be more accurate when supplemented with eGFR results **[31]**.

Another study agreed with this study and demonstrated that levels of CCL2 and its receptor were higher in hemodialyzed cases than in healthy controls, referring to a relationship with the increased risk of developing atherosclerosis in these patients **[32]**.

CCL2 has shown kidney protective properties during acute inflammatory response after renal ischemic/reperfusion injury **[33].** CCL2 is the major cytokine responsible for the recruitment of monocytes to sites of active inflammation and has been indicated to play a major role in the pathogenesis of renal diseases **[34]**. There is evidence that glomerular expression of CCL2 correlates with the degree of renal damage **[35, 36].**

The present study demonstrated that CCL2 in hemodialyzed patients with dyslipidemia was a statistically significant increase when compared to hemodialyzed patients without dyslipidemia ($p=0.008$) which agreed with a previous work that revealed a significantly high level of CCL2 in dyslipidemic subjects **[29]**.

In this study, hemodialyzed patients with dyslipidemia had higher CCL2 when compared to the control group with dyslipidemia ($p<0.001$) which agreed with other reports that had shown, CCL2 plasma levels have been associated with several traditional cardiovascular risk factors such as obesity, age, hypercholesterolemia, hypertension, diabetes, and renal insufficiency **[9]**.

On other hand, another study found that by comparing the mean CCL2 levels in relation to those who had and those who did not have dyslipidemia, it was not possible to observe a statistically significant difference between them. A significant association between CCL2 levels and dyslipidemia was found even after adjustment for possible confounding factors, such as age, sex, BMI, DM, time in HD, pre-HD urea, and inter-dialytic weight gain **[29].**

According to the present research, the receiver operating characteristic (ROC1) curve of the CCL2 level was conducted for discrimination between hemodialyzed patients and the control group. CCL2 showed moderate accuracy, AUC (AUC=0.836). At the best cut-off value of 1060 (pg/ml), sensitivity was 80%, specificity was 85%, PPV was 94.1%, NPV was 58.6% and accuracy was 81.3%. In addition, the ROC2 curve of CCL2 level was conducted for discrimination between dyslipidemia and non-dyslipidemia among all studied subjects. CCL2 showed high accuracy, AUC =0.972, at best cut-off value of 1268 (pg/ml), sensitivity was 92.2%, specificity was 86.2%، PPV was 92.2%, NPV was 86.3% and accuracy was 90%. In addition, the ROC3 curve of CCL2 level was conducted for discrimination between dyslipidemia and non-dyslipidemia among hemodialyzed patients. CCL2 showed high accuracy, AUC =0.968, at best cut-off value of 1278 (pg/ml), sensitivity was 87%, specificity was 100%, PPV was 100%, NPV was 70.1% and accuracy was 90%. When CCL2 was higher than 1278 pg/ml, we can predict dyslipidemia in CKD cases undergoing hemodialysis with a sensitivity of 87% and perfect specificity.

It was found that the analysis of the receiver operating characteristic (ROC) curve for diabetic nephropathy detection showed that the cut-off point of CCL2 serum was 436 pg/ml with a sensitivity of 83.7 % and a specificity of 84.8 %. The AUC, PPV, and NPV levels were determined at 0.886, 72%, and 91.7% respectively **[30]**.

The present study demonstrated that CCL2 showed significant positive correlations with urea, TC, and LDL-c in hemodialyzed patients. While another study found that there was no significant correlation between CCL2 levels with total cholesterol, HDL-c, LDL-c, VLDL-c, non-HDL fraction, or triglycerides **[29]**. On the other hand, a significant positive correlation was found between CCL2 and creatinine **[37]**.

In the current study, CVD risk factors (BMI, DM, HD time, urea, age, and sex) were evaluated whether they could be confounding the association obtained between CCL2 levels and dyslipidemia. CCL2 was considered a risk predictor in the crude model and after adjustment with age and gender, as well as after adjustment with BMI, DM, hemodialysis time, and urea. So, CCL2 was considered an independent risk predictor for dyslipidemia occurrence in hemodialyzed cases even after adjustment with other confounders.

6. Conclusion

In conclusion, our findings show that CCL2 levels are associated with dyslipidemia in hemodialyzed patients even after adjustment for possible confounding factors. This finding may suggest the role of CCL2 in the pathogenesis of atherosclerotic cardiovascular disease in HD patients.

References

[1] S.Ahmadmehrabi, and W.H.W.Tang, Hemodialysis-induced cardiovascular disease DOI: 10.1111/sdi.12694258|©2018 Wiley Periodicals, Inc.wileyonlinelibrary.com/journal/sdi, Seminars in Dialysis,vol.31,pp.258–267,2018.

[2] R.Vanholder, Z.Massy, A.Argiles, G.Spasovski, F.Verbeke, and N.Lameire, Chronic kidney disease as cause of cardiovascular morbidity and mortality, Nephrology Dialysis Transplantation,vol, 20(6),pp.1048–1056,2005.

[3] M.C.Bulbul, T.Dagel, B.Afsar, N.N.Ulusu, M.Kuwabara, A.Covic, Disorders of lipid metabolism in chronic kidney disease. Blood Purif,vol,46 (2),pp.144–152,2018.

[4] D.B.Précoma, G.M.M.de Oliveira, A.F.Simão, O.P.Dutra, O.R.Coelho, M.C.de Oliveira Izar, Updated Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology – 2019. Arq. Bras. Cardiol,vol.113(4),pp. 10.5935:20190204,2019.

[5] B.Lyu, T.Banerjee, J.J.Scialla, T.Shafi, A.S.Yevzlin, N.R.Powe, Vascular calcification markers and hemodialysis vascular access complications. Am. J. Nephrol,vol.48 (5),pp.330–338,2018.

[6] L.P.Gregg, M.C.Tio, X.Li, B.Adams-Huet, J.A.De Lemos, and S.S.Hedayati, Association of monocyte chemoattractant protein-1 with death and atherosclerotic events in chronic kidney disease, Am. J. Nephrol,vol.47(6),pp.395–405,2018.

[7] M.Naito, Macrophage differentiation and function in health and disease, Pathol. Int,vol.58(3),pp.143–155, 2008.

[8] H.R.Vianna, C.M.Soares, K.D.Silveira, G.S.Elmiro, P.M.Mendes, M.S. Tavares, Cytokinesin chronic kidneydisease: potentiallink ofMCP-1 and dyslipidemia in glomerular diseases. Pediatr. Nephrol,vol.28 (3),pp.463–469,2013.

[9] A.Yadav, , V.Saini, , and S.Arora, MCP-1: chemoattractant with a role beyond immunity: a review, Clin. Chim.Acta,vol. 411(21–22),pp.1570–1579,2010.

[10] I.Kazmi, L.Gullapudi, and M. W. Taal, What every doctor needs to know about chronic kidney disease. British Journal of Hospital Medicine,vol.79(8),pp.438-443,2018.

[11] B.Williams, Time to Abandon Clinic Blood Pressure for the Diagnosis of Hypertension?. Circulation,vol. 134 (23),pp.1808-1811,2016.

[12] G.R.Cooper, and V.McDaniel, Manual of Methods for the Determination of Glucose, CDC, USPHS, Atlanta,vol.42,pp.78-95,2011.

[13] D.J.Newman, and C.P.Price Renal function and nitrogen metabolites. In: Burtis CA, Ashwood ER, editors. Tietz Textbook of Clinical Chemistry. 3rd ed. Philadelphia: W.B Saunders Company,vol.475 ,pp.1204-1270,1999.

[14] L.Thomas, Clinical Laboratory Diagnostics. 1st ed. Frankfurt: TH-Books Verlagsgesellschaft ,vol.521,pp.366-374,1998.

[15] H.K.Naito, HDL Cholesterol. Kaplan A et al. Clin Chem. The C.V. Mosby Co., St Louis, Toronto, Princeton,vol. 437,pp.1207-1213,1984.

[16] National Institutes of Health Consensus Development Conference Statement Triglyceride, High Density Lipoprotein and Coronary Heart Disease. Washington D.C,vol.12,pp.26-28,1992.

[17] G.Bucolo, and H.David, Quantitative determination of serum triglycerides by the use of enzymes. Clin Chem,vol.19(5),pp.476-82,1973.

[18] M.Hedayatnia, Z.Asadi,, R.Zare-Feyzabadi, M.Yaghooti-Khorasani, H.Ghazizadeh, R.Ghaffarian-Zirak, Dyslipidemia and cardiovascular disease risk among the MASHAD study population. Lipids Health Dis,vol.19(42),pp.45-52 ,2020.

[19] M.Sampson, C.Ling, Q.Sun, R.Harb, M.Ashmaig, R.Warnick, A New Equation for Calculation of Low-Density Lipoprotein Cholesterol in Patients with Normolipidemia and/or Hypertriglyceridemia. JAMA Cardiol,vol.5(5),pp.1–9,2020.

[20] J.E.Fischer, L.M.Bachman, and R.Jaeschke, A readers' guide to the interpretation of diagnostic test properties: clinical example of sepsis. Intensive Care Med,vol. 29,pp.1043–51,2003.

[21] S.K. Sah, and L.P.Adhikary, Association between Dyslipidemia and Serum Level of 25-Hydroxyvitamin-D in Early Chronic Kidney Disease, Not on Dialysis: An Observational Cross-Sectional Study from the Himalayan Country. Int J Nephrol Renovasc Dis,vol.13,pp.211-218,2020.

[22] J.Puthumana, H.Thiessen-Philbrook, L.Xu, S.G.Coca, A.X.Garg, J.Himmelfarb, Biomarkers of inflammation and repair in kidney disease progression. J Clin Invest,vol.131(3), ,pp.39927,2021.

[23] N.Halbesma, A.H.Brantsma, S.J.Bakker, D.F.Jansen, R.P.Stolk, D.De Zeeuw, Gender differences in predictors of the decline of renal function in the general population. Kidney Int,vol.74(4),pp.505-512,2008.

[24] Noori, N., Hosseinpanah, F., Nasiri, A.A., and Azizi, F. (2009). Comparison of overall

obesity and abdominal adiposity in predicting chronic kidney disease incidence among adultsJ Ren Nutr. 19(3), 228-237.

[25] O.A.Adejumo, E.I.Okaka, and L.I. Ojogwu, Lipid profile in pre-dialysis chronic kidney disease patients in southern Nigeria. Ghana medical journal,vol. 50(1),pp. 44–49,2016.

[26] [26] S.Singh , A.K.Pathak, and N.U.Parappanavar, A study of fasting lipid profile in chronic kidney disease patients. Int J Res Med Sci,vol.7,pp.2282-2285,2019.

[27] S.Chen, C.Hung, M.Kuo, J.Lee, Y.Chiu, J.Chang, Association of Dyslipidemia with Renal Outcomes in Chronic Kidney Disease. PLoS ONE,vol. 8(2),pp.e55643.2013.

[28] M.V.Bhargavi, A case-control study of prevalence and type of dyslipidemia in chronic kidney disease January 2015International Journal of Pharma and Bio Sciences,vol.6(2),pp.93-102,2015.

[29] W.V.De Oliveira Junior, A.P.F.Silva, R.C.de Figueiredo, K.B.Gomes, A.C.S.E.Silva, L.M.S.A.Dusse Association between dyslipidemia and CCL2 in patients undergoing hemodialysis. Cytokine,vol.125,pp.154858,2020.

[30] I.V.G.Schettini, D.V.Faria, L.S.Nogueira, A.Otoni, A.C.S.Silva, , and D.R.A.Rios Renin angiotensin system molecules and chemokine (C-C motif) ligand 2 (CCL2) in chronic kidney disease patients. Braz. Journal of Nephrology. ,vol.(43),pp.3,2021.

[31] A.Lestarini, A.A.S.A.Aryastuti, N.P.D.Witari, I.W.Sutarka, N.W.S.Wardani, P.Hastuti, MCP-1 Serum Levels were Higher in Patient with Diabetic Nephropathy among Balinese, Indian Journal of Public Health Research & Development,vol.11(2),pp.1350-1355,2020.

[32] S.Okumoto, Y.Taniguchi, A.Nakashima, T.Masaki, T.Ito, T.Ogawa, C-C chemokine receptor 2 expression by circulating monocytes influences atherosclerosis in patients on chronic hemodialysis, Ther. Apher. Dial,vol.13 (3) ,pp. 205–212, 2009.

[33] I.Stroo, N.Claessen, G.J.Teske, L.M.Butter, S.Florquin, and J.C.Leemans, Deficiency for the chemokine monocyte chemoattractant protein-1 aggravates tubular damage after renal ischemia/reperfusion injury. PLoS ONE,vol.10,pp.0123203,2015.

[34] K.F. Kusan , K.Nakamura, H.Kusano, N.Nishii, K.Banba, T.Ikeda, Significance of the level of monocyte chemoattractant protein-1 in human atherosclerosis, Circ. J,vol.68 (7),pp.671–676,2004.

[35] S.Paccosi, C.Musilli, G.Mangano, A.Guglielmotti, and A.Parenti, The monocyte chemotactic protein synthesis inhibitor bindarit prevents mesangial cell proliferation and extracellular matrix remodeling, Pharmacol. Res,vol.66 (6),pp.526–535,2012.

[36] S.Paccosi, and A.Parenti, Leukocyte-independent effects of CC-chemokines on vascular remodeling, Curruent. Pharmacol. Biotechnology,vol.19 (9),pp.715–727,2018.

[37] R.E.Silva, E.C.Santos, P.B.I.Justino, M.P.Santos, G.Galdino, R.V.Gonçalves, Cytokines and chemokines systemic levels are related to dialysis adequacy and creatinine clearance in patients with end-stage renal disease undergoing hemodialysis. Int Immunopharmacol,vol.100,pp.108154,2021.