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The protective effect of MCP-1 -2518 A>G promoter polymorphism in Turkish chronic renal failure patients requiring long-term hemodialysis

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Abstract
Objective Monocyte chemoattractant protein-1 (MCP-1) plays a major role in the pathogenesis and progression of different types of human renal disease. Therefore, in this study, we aimed to investigate the effect of MCP-1 gene -2518 A>G promoter polymorphism in chronic renal failure (CRF) patients requiring long-term hemodialysis.
Methods The study population consisted of 201 adult CRF patients requiring long-term hemodialysis and 194 healthy controls. The polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) technique was used for genotyping of MCP-1 -2518 A>G polymorphism in the CRF patients and healthy controls.
Results There were statistically significant differences in terms of genotypic ($\chi^2 = 12.69$, $p = 0.02$) and allelic ($\chi^2 = 5.72$, $p = 0.02$) frequencies of MCP-1 -2518 A>G between CRF patients and control subjects. According to our results, in the patient group MCP-1 -2518 AA genotype frequency was significantly higher than that of control group. On the other hand, heterozygous AG genotype frequency in the control group was significantly higher than that of the study group. Three different main disease subgroups of CRF (hypertension, diabetes mellitus, and atherosclerosis) patients were also evaluated, and significant associations were found between hypertension (genotype: $\chi^2 = 9.28$, $p = 0.01$; allele: $\chi^2 = 6.00$, $p = 0.01$), atherosclerosis (genotype: $\chi^2 = 5.37$, $p = 0.02$; allele: $\chi^2 = 4.13$, $p = 0.04$), and distributions of MCP-1 -2518 A>G genotypes and alleles. However, no significant association was found between diabetes mellitus and distributions of MCP-1 -2518 A>G genotype and allele frequencies (genotype: $\chi^2 = 2.37$, $p = 0.3$; allele: $\chi^2 = 1.88$, $p = 0.17$).
Conclusion Current data show that MCP-1 -2518 AA genotype may cause susceptibility to CRF, while G allele may have a protective effect against development of CRF. In addition, MCP-1 -2518 AA genotype seems to associate with CRF originated from hypertension and atherosclerosis in our study population.

Keywords MCP-1 · Chronic renal failure · Polymorphism · Hypertension · Diabetes mellitus · Atherosclerosis

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Introduction

Inflammatory cells play pivotal roles in renal injury and renal allograft rejection [1, 2]. The presence of leukocytes in the diseased kidneys is a characteristic feature of almost any type of renal disease. Activated leukocytes play an important role in the pathogenesis of kidney diseases [3]. Chemokine-mediated leukocyte recruitment and activation are crucial process in both initiation and progression of renal inflammation [4]. All types of renal cells are able to produce chemokines [5]. In kidney diseases, cytokines and chemokines are also produced by infiltrating leukocytes [6].

Table 1 Clinical and demographic characteristics of CRF patients, CRF subgroups, and healthy controls

Variable	CRF (201)	CRF with DM (58) 28.9 %	CRF with HT (113) 56.2 %	CRF with Atherosclerosis (28) 13.9 %	Control
Average age	57.81 ± 14.18	57.62 ± 8.42	58.07 ± 13.67	57.34 ± 10.13	56.92 ± 9.83
Male %	108 (53.7)	31 (53.45)	46 (40.70)	20 (71.42)	52.9 (101)
Female %	93 (46.3)	27 (46.55)	67 (59.30)	8 (28.58)	47.1 (90)
Parental consanguinity %	21 (10.4)	8 (13.8)	10 (8.84)	3 (10.71)	–
FMF %	2 (1.0)	–	–	–	–

CRF chronic renal failure, *DM* diabetes mellitus, *HT* hypertension, *FMF* familial Mediterranean fever

The monocyte chemoattractant protein-1 (MCP-1) is a potent chemotactic factor for monocytes and a member of the CC chemokine family [7]. MCP-1 is expressed at injury and inflammation sites to direct macrophage recruitment; it binds CC chemokine receptor 2 (CCR2) to promote macrophage adhesion and chemotaxis to disease sites [8]. MCP-1 plays an important role in progression of renal damage by attracting and activating monocytes. MCP-1 also induces the proliferation of both tubular epithelial cells and vascular smooth muscle cells [9–11].

Disease-specific experimental animal models and clinical studies confirmed that MCP-1 plays a crucial role in the pathogenesis of renal diseases. It was shown that deleting MCP-1 considerably reduces macrophage and T cell recruitment, protects renal pathology, reduces proteinuria, and prolongs survival in MCP-1-deficient MRL-Fas(lpr) mice (Lupus-prone mice) [3, 12]. In another animal study conducted using CCR2 knockout mice, nephrotoxic serum has increased the severity of glomerulonephritis in mice, and the authors suggested that CCR2 protein ameliorates glomerulonephritis [13]. In accordance with this study, in our previous study, we found that the CCR2-64I allele was significantly high in chronic renal failure (CRF) patients [14].

An A/G polymorphism was described at the -2518 position of the MCP-1 gene promoter region by Rovin et al. [15]. This polymorphism influences the transcriptional activity of MCP-1 gene. Leukocytes of individuals bearing G/G and A/G genotype of MCP-1 -2518 A/G polymorphism produce significantly higher levels of MCP-1 after inducing with an inflammatory stimulus than those individuals bearing A/A genotype [15, 16]. MCP-1 is expressed in renal tissues, and it is detectable in urine of patients with a variety of renal diseases [17]. One method to detect the expression of MCP-1 in glomerular disease is to measure the levels of MCP-1 in urine, which is high in patients with glomerulopathies [18]. Selective targeting of MCP-1 seems to be an effective treatment in suppressing a number of renal diseases.

In the current study, we aimed to investigate distributions of genotype and allele frequencies of MCP-1 -2518 A>G polymorphism and to demonstrate the possible role of this polymorphism in chronic renal failure patients requiring long-term hemodialysis.

Materials and methods

Study population

Two hundred and forty-two blood samples were collected from patients with chronic renal failure requiring long-term hemodialysis in five different dialysis centers from Sivas, Turkey [19]. Information including history of diabetes mellitus, hypertension, atherosclerosis, renal and cardiac diseases, or family history of renal disease was obtained from patients. Initial patient group consisted of hypertension, diabetes mellitus, atherosclerosis, polycystic kidney, nephrolithiasis, glomerulonephritis, and familial Mediterranean fever (FMF). Forty-one patients having more than one etiologic reasons (diabetes mellitus, hypertension, atherosclerosis, polycystic kidney, nephrolithiasis, glomerulonephritis, and FMF) were excluded from the study. Remaining 201 patients (average age of 57.81 ± 14.18) 108 male and 93 female adult chronic renal failure patients requiring long-term hemodialysis were enrolled in the current study. One hundred and ninety-four age- and sex-matched healthy individuals with no history of diabetes mellitus, hypertension, and renal and cardiac diseases are selected as healthy controls (Table 1).

Genotyping

Peripheral blood samples obtained both from chronic renal failure patients and healthy controls were collected in tubes with EDTA and stored at −20 °C. Total genomic DNA was isolated from a 100-μL peripheral blood sample with an Invitek kit extraction technique (Invisorb spin blood; Invitek, Berlin, Germany). The PCR mixture in a 25-μL final volume consisted of 12.5 μL PCR master mix (Fermentas, Germany), 9.5 μL ddH2O, 1 μL of each primer, and 1 μL DNA. The A to G mutation -2518 of MCP-1 gene was determined by polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) methods.

Table 2 Comparison of MCP-1 -2518 A>G genotype and allele frequencies among CRF patients, CRF subgroups, and healthy controls

Genotype	CRF (191) (*n*) %	CRF with DM (58) (*n*) %	CRF with HT (113) (*n*) %	CRF with Atherosclerosis (28) (*n*) %	Control (194) (*n*) %
AA	(103) 51.25	(26) 44.8	(59) 52.2	(15) 53.6	(67) 34.54
AG	(79) 39.3	(29) 50.0	(46) 40.7	(13) 46.4	(110) 56.7
GG	(19) 9.45	(3) 5.2	(8) 7.1	(0) 0.0	(17) 8.76
p value	χ^2: 12.69, *p:* 0.02	χ^2: 2.37, *p:* 0.3	χ^2: 9.28, *p:* 0.01	χ^2: 5.37, *p:* 0.02	–
Allele					
A	(285) 70.9	(81) 69.8	(164) 72.6	(43) 76.8	(244) 62.9
G	(117) 29.1	(35) 30.2	(62) 27.4	(13) 23.2	(144) 37.1
p value	χ^2: 5.72, *p:* 0.02	χ^2: 1.88, *p:* 0.17	χ^2: 6.00, *p:* 0.01	χ^2: 4.13, *p:* 0.04	–

CRF chronic renal failure, *DM* diabetes Mellitus, *HT* hypertension

The following primers were used for amplification: forward 5′-TCTCTCACGCCAGCACTGACC-3′ and reverse 5′-GAGTGTTCACATAGGCTTCTG -3′. Initial denaturation step at 95 °C for 3 min was followed by 35 cycles of denaturation at 95 °C for 45 s, annealing at 55 °C for 45 s, and extension at 72 °C for 45 s. Final extension step was at 72 °C for 5 min.

PCR product (5 µl) was digested 16 h at 37 °C with 2.5U of PvuII restriction endonuclease (Fermentas, Germany). Digestion products were analyzed by electrophoresis on 2 % agarose gel in TBE buffer and visualized using ethidium bromide staining. Samples with a single 234-bp band were identified as having AA genotype, samples with two bands 159 and 75 bp as GG genotype, and those with three bands 234, 159, and 75 bp as AG heterozygote.

Statistical analysis

Statistical analysis was performed using SPSS statistical package software, version 16.0 (SPSS Inc., Chicago, USA). Mean age in the two groups was compared by Student's *t* test. Differences in the genotype and allele distribution of MCP-1 -2518 A/G polymorphism between CRF patients, CRF subgroups, and healthy controls were tested using Pearson Chi-square test. Results were considered significant when the *p* value (two-tailed) was less than 0.05. Odds ratios with 95 % confidence intervals (CI) estimated the effect of MCP-1 -2518 high-risk allele.

Results

Clinical and demographic characteristics of patients and control group are shown in Table 1. Hypertension, diabetes mellitus, and atherosclerosis were found in 56.2, 28.9, and 13.9 % of the patients, respectively. 10.4 % of patients have parental consanguinity, and two patients have FMF. Demographic characteristics of disease subgroups are also shown Table 1. There was not any renal disease in all of our selected 201 patients before chronic renal failure.

For the entire group of patients with CRF, the frequencies of AA, AG, and GG genotypes of MCP-1 gene were 51.25 % ($n = 103$), 39.3 % ($n = 79$), and 9.45 % ($n = 19$), respectively. Distribution of MCP-1 -2518 A>G promoter polymorphisms (AA, AG, GG) in healthy controls was 34.54 % ($n = 67$), 56.7 % ($n = 110$), and 8.76 % ($n = 17$), respectively (Table 2). There was statistically significant difference in terms of genotypic ($\chi^2 = 12.69$, $p = 0.02$) and allelic ($\chi^2 = 5.72$, $p = 0.02$) frequencies of MCP-1 -2518 A>G polymorphism between CRF patients and control subjects. Three different main disease subgroups of CRF (hypertension, diabetes mellitus, and atherosclerosis) patients were also compared with healthy controls, and significant associations were found between MCP-1 -2518 A>G polymorphism and two disease groups: hypertension (genotype: $\chi^2 = 9.28$, $p = 0.01$; allele: $\chi^2 = 6.00$, $p = 0.01$) and atherosclerosis (genotype: $\chi^2 = 5.37$, $p = 0.02$; allele: $\chi^2 = 4.13$, $p = 0.04$). However, no significant association was found between diabetes mellitus and distributions of MCP-1 -2518 A>G genotype and allele frequencies (genotype: $\chi^2 = 2.37$, $p = 0.3$; allele: $\chi^2 = 1.88$, $p = 0.17$) (Table 2).

Compared with the AG and GG, AA genotype had twofold higher risk of the development of CRF in patient group. On the other hand, in the control group, compared with GG and AA genotypes, AG has twofold protective effect (Table 3).

Discussion

Numerous evidences revealing the importance of MCP-1 in pathogenesis of renal diseases have been reported until today. Some of these studies include demonstration of relationships between MCP-1 gene and renal damage in animal models, while others include studies on MCP-1 gene expression and mutations in different types of human renal diseases [5].

Table 3 Risk estimate for MCP-1 -2518 A>G genotypes in CRF patients

MCP-1	Odds ratio	95 % Confidence interval		*p*
		Lower	Upper	
AA versus AG + GG	1.9922	1.3287	2.9872	0.0009
GG versus AA + AG	1.0869	0.5472	2.1590	NS
AA + GG versus AG	2.0223	1.3543	3.0198	0.0006

NS not significant

Locally produced MCP-1 contributes both initiation and progression of tubulointerstitial damage. Tesch et al. have shown that transgenic MCP-1-deficient mice with nephrotic serum-induced nephritis exhibit less tubulointerstitial lesions, compared with wild-type mice, but they exhibit no differences in glomerular lesions [20]. Viedt et al. [10] have found that MCP-1 is able to directly upregulate the pro-inflammatory cytokine IL-6 and the adhesion molecule ICAM-1.

MCP-1 shows its effect through the CCR2 receptor. There are two isoforms of CCR2, namely CCR2A and CCR2B. It is thought that CCR2A and CCR2B use different signaling pathways and cause different movements [7]. While MCP-1 chemotaxis of CCR2A-positive cells occurs without Ca^{+2} mobilization, in the CCR2B-positive cells, Ca^{+2} flux is induced [7, 20, 21]. CCR2 plays a dual role due to both its pro-inflammatory and anti-inflammatory effects in the pathogenesis of diseases. The pro-inflammatory role of CCR2 depends on antigen-presenting cells (APCs) and T cells; on the other hand, the anti-inflammatory role of CCR2 depends on expression of CCR2 in regulatory T cells [7].

Similar to our study, in 201 Caucasian patients with IgA nephropathy, Steinmetz et al. [22] found the distribution of AA, AG, and GG genotypes as 53.6, 40.1, and 6.3 %, respectively. However, they have not determined a relationship between MCP-1 -2518 A>G polymorphism, predisposition to IgA nephropathy, and prognosis of this disease. Mori et al. [9] have investigated the effect of MCP-1 gene polymorphism in 277 Japanese patients diagnosed with IgA nephropathy and found that the incidence of end-stage renal disease (ESRD) was significantly higher in patients with the AA genotype (47.1 %) compared to those with the AG (24.1 %) or GG (27.4 %) genotype. Moreover, they found that AA genotype represented a twofold risk of the progression of renal disease compared to the AG/GG genotype. Therefore, they suggested that the AA genotype at MCP-1 -2518 A>G was an independent risk factor for the progression of renal disease in Japanese patients with IgA nephropathy and was closely associated with renal survival. In our study, the AA genotype was higher than other genotypes in the patient group.

Malafronte et al. have found the higher frequency of MCP-1 -2518 GG genotype in 197 patients with lupus nephritis than healthy controls. However, there was no association of this genotype with renal function or renal survival in Malafronte et al.'s study [23]. Similar to results of Malafronte et al.'s study, Buraczynska et al. [24] have compared frequencies of MCP-1 -2518 A>G polymorphisms in hemodialyzed patients with cardiovascular disease (CVD), hemodialyzed patients without CVD, and healthy controls. In this study, G allele was observed significantly higher frequency in patients with CVD. There was no statistically significant difference in the distribution of MCP-1 genotypes between ESRD patients without CVD and healthy controls in this study. Results of Buraczynska et al.'s study indicate that MCP-1 -2518 G allele generates susceptibility to CVD in hemodialyzed patients. Similarly, high frequency of MCP-1 -2518 G allele has been found in Egyptian glomerulonephropathy patients compared with healthy controls by Hassan et al. [25]. Krüger et al. [26] have investigated the impact of the MCP-1 -2518G and CCR2 64I genotypes on renal allograft function in 232 patients who underwent transplantation over an 11-year period. Results of this study have revealed that recipients of renal transplants homozygous for the -2518G mutation of the MCP-1 gene are at risk of premature kidney graft failure. However, Lehmann et al. [27] have researched the impact of the MCP-1 -2518 A>G polymorphism in donor cells on renal allograft outcomes and have found that the MCP-1 polymorphism of the donor has no impact on the allograft outcome during the first year after transplantation. Inconsistent results in all of these studies may be caused by population-dependent difference of distribution of MCP1 -2518 A>G genotypes and/or phenotypic specificity of this genotypes.

Our study group has involved the main disease subgroups: hypertension, atherosclerosis, and diabetes mellitus. We analyzed genotypic and allelic frequencies of MCP-1 polymorphism in this three disease subgroups. Increased glucose levels were shown to stimulate MCP-1 production in human and mouse mesangial cells as well as kidney epithelial cells, including glomerular podocytes and tubular cells. Elevated MCP-1 stimulates inflammation, progressive injury, and renal fibrosis in diabetic kidneys [28]. No significant association was found between diabetes mellitus and distributions of MCP-1 -2518 A>G genotype and allele frequencies (genotype: $\chi^2 = 2.37$, $p = 0.3$; allele: $\chi^2 = 1.88$, $p = 0.17$) in the current study. Joo et al. [29] have studied MCP-1 -2518 A>G gene polymorphism in 177 patients with diabetic ESRD due to type 2 diabetes, and they have not found any significant association between this polymorphism and diabetic ESRD. Moon et al. [30] have investigated MCP-1 gene -2518 A>G polymorphism in type 2 DM patients with progressive kidney

failure compared with matched type 2 DM patients without nephropathy (diabetic control) and healthy controls. Although they have not found a statistically significant difference between genotype frequencies of patients with progressive kidney failure and healthy controls, they found that the MCP-1 -2518 A allele was more frequent in patients with kidney failure than in DM controls. They suggest that carriage of -2518 A allele is associated with kidney failure in Korean patients with type 2 DM. Different results was found for these diseases depending on study population. In Japanese population, MCP-1 polymorphism was not found to be associated with type 2 diabetes. But in obese diabetic subgroup of this study, -2518 AA cases had increased insulin resistance than obese diabetic -2518G carriers [31].

MCP-1 plays an important role in atherosclerosis with its ability to stimulate monocyte recruitment, differentiation to foam cells, and proliferation of smooth muscle cells [11, 32]. In a study on diabetic coronary artery disease susceptibility and MCP-1 mutation frequency, Bagci et al. [33] found that MCP-1 -2518 AA genotype may cause diabetic coronary artery disease susceptibility in a Turkish population. Kaur et al. [34] demonstrated that MCP-1 -2518 G allele is associated with increased risk of coronary artery disease and reduced risk of type 2 diabetes in the population of Punjab (eastern Pakistan and northern India). Tabara et al. [35] did not found an association with MCP-1 -2518 A>G polymorphism and carotid atherosclerosis in the Japanese population. Yuasa et al. [36] investigated MCP-1 -2518 A>G polymorphisms and atherosclerosis in patients with type 2 diabetes and found that AG or GG genotype was significantly greater than the AA genotype in type 2 diabetic patients developing carotid atherosclerosis in Japanese population. In the current study, we compared MCP-1 -2518 A>G genotype and allele frequencies of patients with atherosclerosis and healthy controls and found that MCP-1 -2518 A allele was significantly higher in patients with atherosclerosis (genotype: $\chi^2 = 5.37$, $p = 0.02$; allele: $\chi^2 = 4.13$, $p = 0.04$).

Like atherosclerosis, hypertension was supposed to be associated with vascular inflammatory response characterized by recruitment of macrophages into the arterial wall [37]. Capers et al. [38] demonstrated that MCP-1 expression was upregulated in arteries of hypertensive rats. In hypertensive ischemic heart disease asymptomatic subjects, it was demonstrated that mutant G allele has been resulted in higher levels of both values of blood pressure, systolic and diastolic than subjects with allele A [39]. We compared MCP-1 -2518 A>G genotype and allele frequencies of patients with hypertension and healthy controls and found that MCP-1 -2518 A allele was significantly higher in patients with hypertension (genotype: $\chi^2 = 9.28$, $p = 0.01$; allele: $\chi^2 = 6.00$, $p = 0.01$).

According to our results, in the patient group, MCP-1 -2518 AA genotype frequency was significantly higher than that of control group. Results of our study showed that AA genotype may increase susceptibility to development of CRF approximately twofold; on the other hand, AG genotype may provide twofold protection against the development of CRF. Current data show that AA genotype may cause susceptibility to CRF, while G allele may have a protective effect. Although no significant association was found between MCP-1 -2518 A>G polymorphism and DM, statistically significant associations were found between MCP-1 -2518 A>G polymorphism and patients with hypertension and atherosclerosis.

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