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Monocyte chemoattractant protein-1 gene (*MCP-1*-2518 A/G) polymorphism and serological markers of hepatitis B virus infection in hemodialysis patients

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Study Design A
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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The role of *MCP1*-2518 A/G in hepatitis B virus (HBV) infection is controversial. Our aim was to evaluate the frequency distribution of *MCP1*-2518 A/G (rs1024611) polymorphic variants in hemodialysis (HD) patients without or with type 2 diabetes in relation to serological markers of HBV infection.

Material/Methods: HD patients (n=170, 48 with diagnosis of type 2 diabetes), who tested positive for total antibodies to HBV core antigen (anti-HBc), underwent *MCP1* genotyping using polymerase chain reaction-restriction fragment length polymorphism assay. Anti-HBc was accompanied by antibodies to HBV surface antigen (anti-HBs) in 127 individuals. In anti-HBc-positive/anti-HBs-negative patients, HBV surface antigen (HBsAg) was shown in 15 patients and isolated anti-HBc were present in 28 patients. The distribution of *MCP1* genotypes in anti-HBc-positive patients was compared to that in healthy subjects (n=437) and anti-HBc-negative HD patients (n=754).

Results: There were no significant differences (P_{trend} >0.05) in distribution of *MCP1* genotypes between anti-HBc-positive patients, anti-HBc-negative subjects, and controls, regardless of anti-HBs or diabetic status. The *MCP1*-2518G allele prevalence was higher in HBsAg-positive/anti-HBs-negative patients defined as HBV carriers compared to *MCP1*-2518G allele frequency shown in groups composed of HBsAg-negative HD individuals and controls (50% *vs.* 28%, P_{trend} 0.022).

Conclusions: A frequency distribution of *MCP1* polymorphic variants is not associated with anti-HBs development in response to HBV infection in HD patients, independent of diabetic status, but the *MCP1*-2518G allele may predispose to HBsAg persistence (HBV carrier status).

MeSH Keywords: **Chemokine CCL2 • Diabetes Complications • Dialysis • Hepatitis B Antibodies • Polymorphism, Genetic**

Abbreviations: **ALT** – alanine aminotransferase; **anti-HBc** – antibodies to core antigen of hepatitis B virus; **anti-HBs** – antibodies to surface antigen of hepatitis B virus; **AST** – aspartate aminotransferase; **cccDNA** – covalently closed circular DNA; **CI** – confidence interval; **DM** – diabetes mellitus; **DNA** – deoxyribonucleic acid; **GGT** – gamma-glutamyltranspeptidase; **HBsAg** – surface antigen of hepatitis B virus; **HBV** – hepatitis B virus; **HD** – hemodialysis; **HWE** – Hardy-Weinberg equilibrium; **IL** – interleukin; **MAF** – minor allele frequency; **MCP-1** – monocyte chemoattractant protein-1; ***MCP1*** – monocyte chemoattractant protein-1 gene; **OR** – odds ratio; **RRT** – renal replacement therapy; **TNF-α** – tumor necrosis factor interleukin

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Background

Patients undergoing chronic hemodialysis (HD) treatment due to end-stage renal disease (ESRD) are at risk of infection with blood-borne viruses, including hepatitis B virus (HBV). Total antibodies to HBV core antigen (anti-HBc) are an established marker of current (IgM) or previous (IgG) infection with HBV if they are positive in the confirmatory tests and reactive in determinations repeated over time [1,2]. Anti-HBc appear as a result of HBV transmission to non-vaccinated or non-successfully hepatitis B vaccinated individuals, but they may also elicit in vaccinated HD patients with maintained protective levels (>10 U/l) of antibodies to HBV surface antigen (anti-HBs) [3]. Immune tolerance to viral antigens, like HBV surface antigen (HBsAg), results in a lack of development of anti-HBs and persistence of HBsAg in the bloodstream. Patients who are HBsAg-positive and simultaneously anti-HBs-negative are commonly defined as HBV carriers. The mechanisms responsible for promotion or inhibition of anti-HBs generation and HBsAg clearance are not fully understood. Monocyte chemoattractant protein-1 (MCP-1), referred also as chemokine (C-C motif) ligand 2 (CCL2), has been suggested to be a link in the chain involved in the hepatitis B outcome [4,5].

Individuals with occult hepatitis B – defined as the presence of HBV DNA in liver/serum with undetectable HBsAg – had significantly increased levels of MCP-1 compared to the healthy controls and patients that had resolved HBV infection (HBsAg-negative, anti-HBs-positive) [5]. MCP-1 expression level in the liver was higher in chronic hepatitis B complicated with non-alcoholic fatty liver diseases than that shown in hepatitis B without such concomitant diseases [6]. MCP-1 was significantly up-regulated in patients with hepatocellular carcinoma, showing HBV infection in over 50% of cases [7]. These data indicate that higher MCP-1 level is generally associated with worse clinical condition in HBV infection. Serum levels of MCP-1 increase with deterioration of renal function and are higher in HD patients than in healthy individuals [8–12]. The promoter region of the MCP-1 gene (*MCP1*) was shown to influence MCP-1 expression [13,14]. The *MCP1*-2518G allele was associated with up-regulation of both MCP-1 transcript and protein levels in many studies [11,13–16], but not all [17]. HD subjects with AG+GG genotypes of the MCP-1 gene (*MCP1* rs1024611) had higher MCP-1 levels than those with the AA variant [11]; this may predispose HD patients to HBV infection. In the study by Park et al. [18] on Korean subjects, promoter polymorphism of *MCP1* (*MCP1*-2518G>A) was involved in HBV clearance, but Cheong et al. [19] did not demonstrate an association of *MCP1*-2518G>A with the outcome of HBV infection in Korean patients.

The aim of our study was to evaluate the frequency distribution of *MCP1*-2518 A/G (rs1024611) polymorphic variants in patients who are non-hepatitis B vaccinated and HBV-infected HD patients in respect to commonly used HBV serological markers present in response to HBV infection. In particular, we would like to determine whether *MCP1*-2518 A/G polymorphism is associated with the development of anti-HBs that usually follows HBsAg disappearance from the bloodstream, and spontaneous recovery from HBV infection indicated by negative HBsAg and positive anti-HBs.

Material and methods

Patients and controls

One hundred seventy HD patients showing positive total anti-HBc were enrolled into the study (99 men, age 61.0±14.7 years, renal replacement therapy vintage 3.1, 0.05–26.3 years). Subjects with isolated anti-HBc positivity (HBsAg-negative, anti-HBc-positive, anti-HBs-negative) were also included. Only patients who had confirmatory assays and consistently maintained positive anti-HBc status were enrolled.

Anti-HBc-positive patients were never hepatitis B vaccinated and accounted for 18.4% of HD subjects (n=924) tested for serologic markers of HBV infection. Thirteen patients had a history of acute hepatitis B. Anti-HBc was accompanied by anti-HBs in 127 individuals: 126 patients showed classical serologic pattern of HBV resolution (HBsAg-negative, anti-HBs-positive), indicating spontaneous recovery from HBV infection; 1 patient in this group was both HBsAg- and HBV DNA-positive. In anti-HBc-positive/anti-HBs-negative patients (n=43), HBsAg positivity was shown in 15 patients (classical serologic pattern of HBV carrier status), and isolated anti-HBc seropositivity (HBsAg-negative, anti-HBc-positive, anti-HBs-negative) was present in 28 patients. HBV DNA testing (detection limit 250 copies ml-1) was positive in 11 HBV carriers (1 patient had a negative test result for HBV DNA, and 3 patients were not investigated). All HBsAg-positive patients (n=16) accounted for 1.7% of all tested subjects.

In the anti-HBc-positive HD group there were 48 patients with type 2 diabetes mellitus (DM), and no patients with type 1 DM. Type 2 DM was a cause of diabetic nephropathy leading to ESRD and HD treatment in all 48 patients. Selected demographic and clinical data of main groups of anti-HBc-positive HD patients are shown in Table 1.

Unrelated blood donors and healthy volunteers served as controls for distribution of *MCP1*-2518 A/G (rs1024611) polymorphic variants (n=437). This control group was also used in our earlier studies [20,21]. Additionally, results of MCP1 genotype distribution in anti-HBc-positive HD patients were compared to those of anti-HBc-negative HD patients (n=754) described

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Table 1. Selected demographic and clinical data of main groups of anti-HBc positive HD patients.

All anti-HBc positive HD patients (n=170)			
Parameter	**Anti-HBs positive (n=127)**	**Anti-HBs negative (n=43)**	**P value**
Men, n (% of all)	71 (55.9)	28 (65.1)	0.371[a]
Age, years	61.6±14.4	59.3±15.5	0.391[b]
RRT duration, years	2.8 (0.05–26.3)	3.6 (0.05–25.1)	0.139[c]
Causes of end-stage renal disease, n (% of all)			
Diabetic nephropathy	37 (29.1)	11 (25.6)	0.700[a]
Hypertensive nephropathy	20 (15.7)	6 (14.0)	0.778[d]
Chronic glomerulonephritis	18 (14.2)	14 (32.6)	**0.008[d]**
Chronic tubulointerstitial nephritis	10 (7.9)	3 (7.0)	0.888[e]
Polycystic kidney disease	7 (5.5)	1 (2.3)	0.663[e]
346[g], 1752[g], 3691[g], 1884[g] or other	35 (27.6)	8 (18.6)	0.311[a]
ALT (U/L)	16 (2–195)	18 (4–53)	0.446[f]
AST (U/L)	18 (6–152)	18 (6–81)	0.651[f]
GGT (U/L)	26 (4–498)	25 (7–284)	0.936[f]
Anti-HBs positive (n=127)			
Parameter	**Diabetics (n=37)**	**Non-diabetics (n=90)**	**P value**
Men, n (% of all)	18 (48.6)	53 (58.9)	0.329[a]
Age, years	63.3±13.1	60.8±14.9	0.381[b]
RRT duration, years	2.0 (0.05–15.7)	3.4 (0.14–26.3)	**0.008[c]**
Causes of end-stage renal disease, n (% of all)			
Diabetic nephropathy	37 (100)	0 (0)	
Chronic glomerulonephritis	–	18 (20.0)	–
Hypertensive nephropathy	–	20 (22.2)	–
Chronic tubulointerstitial nephritis	–	10 (11.1)	–
Polycystic kidney disease	–	7 (7.8)	–
346[g], 1752[g], 3691[g], 1884[g] or other	–	35 (38.9)	–
ALT (U/l)	18 (2–195)	14 (2–95)	0.315f
AST (U/l)	18 (9–152)	17.5 (6–72)	0.588f
GGT (U/l)	25 (12–168)	27 (4–498)	0.944f
Anti-HBs negative (n=43)			
Parameter	**Diabetics (n=11)**	**Non-diabetics (n=32)**	**P value**
Men, n (% of all)	6 (54.5)	22 (68.8)	0.627[e]
Age, years	64.7±12.4	57.5±16.2	0.189[b]
RRT duration, years	3.6 (0.24–24.2)	4.7 (0.05–25.1)	0.770[c]

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Table 1 continued. Selected demographic and clinical data of main groups of anti-HBc positive HD patients.

Anti-HBs negative (n=43)			
Parameter	**Diabetics (n=11)**	**Non-diabetics (n=32)**	**P value**
Causes of end-stage renal disease, n (% of all)			
Diabetic nephropathy	11 (100)	0 (0)	
Chronic glomerulonephritis	–	14 (43.8)	–
Hypertensive nephropathy	–	6 (18.8)	–
Chronic tubulointerstitial nephritis	–	3 (9.4)	–
Polycystic kidney disease	–	1 (3.1)	–
1752[g], 2578[g], 1832[g], 1396[g] or other	–	8 (25.0)	–
ALT (U/l)	18 (8–45)	17.5 (4–53)	0.738[f]
AST (U/l)	19 (11–81)	17 (6–52)	0.549[f]
GGT (U/l)	23 (11–93)	35 (7–284)	0.684[f]

ALT – alanine aminotransferase; anti-HBc – antibodies to core antigen of hepatitis B virus; anti-HBs – antibodies to surface antigen of hepatitis B virus; AST – aspartate aminotransferase; GGT – gamma-glutamyltranspeptidase; HD – hemodialysis; RRT – renal replacement therapy. Statistical tests: a – Chi square; b – t student; c – Mann Whitney; d – V square; e – Yates corrected Chi-square; f – Mann Whitney; g – renal diagnosis codes for the ERA-EDTA [58]. Significant differences are indicated using bold font.

in our recent study [21]. The latter group consisted of 601 anti-HBs-positive patients due hepatitis B vaccination and 153 non-responders to hepatitis B vaccination (anti-HBs-negative).

All examined subjects were of white race.

Genotyping

MCP1 rs1024611 genotyping was determined by polymerase chain reaction-restriction fragment length polymorphism, as previously described [20].

Laboratory methods

Serologic markers of HBV infection and serum activities of liver enzymes were determined by the methods previously described [22].

Statistical methods

Results are presented as percentage for categorical variables, as mean with 1 standard deviation for normally distributed continuous variables, or as median with range for not normally distributed continuous variables. Statistical tests used for comparison of data obtained in selected groups are indicated at each P value.

Hardy-Weinberg equilibrium (HWE) was tested to compare the observed genotype frequencies to the expected ones using the chi-square test. The Fisher exact probability test or chi-square test were used to evaluate differences in genotype and allele prevalence between the examined groups. The odds ratio (OR) with p value and 95% confidence intervals (95% CI) value were calculated. Polymorphisms were tested for association using the chi-square test for trend (P_{trend}). The Fisher exact test was used for power analysis.

Values of $P<0.05$ were judged to be significant. All probabilities were 2-tailed.

Statistical calculations were performed using GraphPad InStat 3.10, 32 bit for Windows, created July 9, 2009 (GraphPad Software, Inc., La Jolla, USA), CytelStudio version 10.0, created January 16, 2013 (CytelStudio Software Corporation, Cambridge, USA), and Statistica version 10, 2011 (Stat Soft, Inc., Tulsa, USA).

Ethical approval

The research design was approved by the Institutional Review Board of Poznań University of Medical Sciences, Poland. Informed consent was obtained from all study participants.

Results

There was no significant deviation from the HWE in the genotype frequencies in all anti-HBc-positive HD patients, non-DM and DM groups, as well as anti-HBs-positive and anti-HBs-negative groups (Supplementary Table 1).

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Table 2. Comparison of the distribution of *MCP1* rs1024611 polymorphic variants in anti-HBc positive/anti-HBs positive hemodialysis (HD) patients and controls

Genotype	Anti-HBc positive/ anti-HBs positive patients (frequency)	Controls (frequency)	Odds ratio (95%CI)	Two-tailed P	P_{trend}	$P_{genotyping}$	Power (%)
All HD cases *vs.* controls							
	n=127	**n=437**					
AA	67 (0.53)	225 (0.51)	Referent	–	0.979	0.796	
AG	48 (0.38)	177 (0.41)	0.911 (0.584–1.414)	0.743			6.3
GG	12 (0.09)	35 (0.08)	1.151 (0.514–2.428)	0.821			6.1
AG+GG	60 (0.47)	212 (0.49)	0.950 (0.627–1.439)	0.881			5.0
MAF	72 (0.28)	247 (0.28)	1.004 (0.725–1.382)	1.000			4.6
HD cases without DM *vs.* controls							
	n=90	**n=437**					
AA	50 (0.56)	225 (0.51)	Referent	–	0.667	0.681	
AG	32 (0.36)	177 (0.41)	0.814 (0.483–1.356)	0.478			10.7
GG	8 (0.09)	35 (0.08)	1.029 (0.388–2.437)	1.000			4.0
AG+GG	40 (0.44)	212 (0.49)	0.849 (0.523–1.373)	0.557			10.6
MAF	48 (0.27)	247 (0.28)	0.923 (0.628–1.340)	0.738			6.4
HD cases with DM *vs.* controls							
	n=37	**n=437**					
AA	17 (0.46)	225 (0.51)	Referent	–	0.446	0.743	
AG	16 (0.43)	177 (0.41)	1.196 (0.548–2.597)	0.751			7.2
GG	4 (0.11)	35 (0.08)	1.513 (0.349–5.009)	0.659			4.9
AG+GG	20 (0.54)	212 (0.49)	1.249 (0.603–2.612)	0.634			8.2
MAF	24 (0.32)	247 (0.28)	1.218 (0.700–2.071)	0.523			11.2

anti-HBc – antibodies to core antigen of hepatitis B virus; anti-HBs – antibodies to surface antigen of hepatitis B virus; DM – diabetes mellitus; MAF – minor allele frequency.

Statistical analyses did not show significant differences in *MCP1* genotype frequencies between anti-HBc-positive HD patients and controls, independent of occurrence of type 2 DM or anti-HBs status (Tables 2 and 3). There were also no significant differences in *MCP1* genotype frequencies when anti-HBc-positive patients were categorized as anti-HBs-positive or -negative (Table 4). Similar comparisons between anti-HBc-positive and anti-HBc-negative HD groups did not reveal a significant difference (P_{trend} >0.05, Supplementary Tables 2–4). *MCP1* genotype frequencies between HD patients with isolated anti-HBc positivity and HD patients with HBV resolution (in our study both these groups differed only in anti-HBs status) were also non-significant (Supplementary Table 5).

The significant differences in *MCP1* genotype frequencies were shown between the anti- HBc-positive HD group that represented HBV carriers and HD individuals with HBV resolution (Table 5), as well as between HBV carriers, healthy controls,

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Table 3. Comparison of the distribution of *MCP1* rs1024611 polymorphic variants in anti-HBc positive/anti-HBs negative hemodialysis (HD) and controls

Genotype	Anti-HBc positive/anti-HBs negative HD patients (frequency)	Controls (frequency)	Odds ratio (95%CI)	Two-tailed P	P_{trend}	$P_{genotyping}$	Power (%)
All HD cases *vs.* controls							
	n=43	**n=437**					
AA	20 (0.47)	225 (0.51)	Referent	–	0.402	0.663	
AG	18 (0.42)	177 (0.41)	1.144 (0.552–2.354)	0.818			5.6
GG	5 (0.11)	35 (0.08)	1.607 (0.442–4.796)	0.525			13.3
AG+GG	23 (0.53)	212 (0.49)	1.221 (0.621–2.417)	0.643			7.5
MAF	28 (0.32)	247 (0.28)	1.225 (0.733–2.008)	0.470			13.1
HD cases without DM *vs.* controls							
	n=32	**n=437**					
AA	16 (0.50)	225 (0.51)	Referent	–	0.611	0.669	
AG	12 (0.38)	177 (0.41)	0.953 (0.401–2.211)	1.000			4.5
GG	4 (0.13)	35 (0.08)	1.607 (0.369–5.374)	0.595			13.4
AG+GG	16 (0.50)	212 (0.49)	1.061 (0.483–2.330)	1.000			4.6
MAF	20 (0.31)	247 (0.28)	1.154 (0.631–2.046)	0.702			7.3
HD cases with DM *vs.* controls							
	n=37	**n=437**					
AA	4 (0.36)	225 (0.51)	Referent	–	0.405	0.602	
AG	6 (0.55)	177 (0.41)	1.907 (0.444–9.317)	0.494			13.9
GG	1 (0.09)	35 (0.08)	1.607 (0.032–16.83)	1.000			5.7
AG+GG	7 (0.64)	212 (0.49)	1.857 (0.464–8.767)	0.494			12.2
MAF	8 (0.36)	247 (0.28)	1.451 (0.520–3.758)	0.540			11.5

anti-HBc – antibodies to core antigen of hepatitis B virus; anti-HBs – antibodies to surface antigen of hepatitis B virus; DM – diabetes mellitus; MAF – minor allele frequency.

anti-HBc negative HD patients, and HD patients with isolated anti-HBc positivity (Table 6). There was a higher prevalence of the *MCP1*-2518G allele in HBV carriers compared to the *MCP1*-2518G allele frequency in patients of all aforementioned groups. Among anti-HBc-positive HD patients, the highest prevalence of HBsAg-positive/anti-HBs-negative subjects (HBV carriers) was in the group bearing the GG genotype (Supplementary Table 6).

Discussion

The past decades have brought important changes in recognition of outcome of HBV infection. A discovery of HBV covalently closed circular DNA (cccDNA) organized into minichromosomes within the nucleus of HBV-infected cells have presented new challenges for researchers and clinicians who focus on complete cccDNA eradication as a target for antiviral

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Table 4. Comparison of the distribution of *MCP1* rs1024611 polymorphic variants in anti-HBc positive/anti-HBs negative patients hemodialysis (HD) and anti-HBc positive/anti-HBs positive HD patients.

Genotype	Anti-HBc positive/anti-HBs negative patients (frequency)	Anti-HBc positive/anti-HBs positive patients (frequency)	Odds ratio (95%CI)	Two-tailed P	P_{trend}	$P_{genotyping}$	Power (%)
All HD cases							
	n=43	**n=127**					
AA	20 (0.47)	67 (0.53)	Referent	–	0.473	0.766	
AG	18 (0.42)	48 (0.38)	1.256 (0.560–2.798)	0.673			7.7
GG	5 (0.11)	12 (0.09)	1.396 (0.342–4.911)	0.772			8.0
AG+GG	23 (0.53)	60 (0.47)	1.284 (0.606–2.732)	0.595			8.5
MAF	28 (0.33)	72 (0.28)	1.220 (0.690–2.125)	0.542			10.4
HD cases without DM							
	n=32	**n=90**					
AA	16 (0.50)	50 (0.56)	Referent	–	0.504	0.790	
AG	12 (0.38)	32 (0.36)	1.172 (0.442–3.039)	0.888			5.9
GG	4 (0.13)	8 (0.09)	1.563 (0.302–6.791)	0.734			8.7
AG+GG	16 (0.50)	40 (0.44)	1.250 (0.514–3.036)	0.736			6.8
MAF	20 (0.31)	48 (0.27)	1.250 (0.631–2.421)	0.534			9.8
HD cases with DM							
	n=11	**n=37**					
AA	4 (0.36)	17 (0.46)	Referent	–	0.727	0.803	
AG	6 (0.55)	16 (0.43)	1.594 (0.306–9.097)	0.784			6.1
GG	1 (0.09)	4 (0.11)	1.063 (0.017–15.84)	1.000			1.9
AG+GG	7 (0.64)	20 (0.54)	1.488 (0.310–8.103)	0.836			6.4
MAF	8 (0.36)	24 (0.32)	1.190 (0.378–3.544)	0.919			5.1

anti-HBc – antibodies to core antigen of hepatitis B virus; anti-HBs – antibodies to surface antigen of hepatitis B virus; DM – diabetes mellitus; MAF – minor allele frequency.

therapy [23,24]. Therefore, disappearance of cccDNA from infected cells (hepatocytes) could be an indicator of resolution of HBV infection. Commonly used serologic markers of HBV infection help to stratify the HBV-infected individuals according to their infectivity rather than in respect to HBV eradication and total dissolution of hepatitis B infection. They change over time and may disappear throughout the lifespan. Such a possibility needs to be taken into account in stratification of infected patients for those with a high probability of HBV replication (HBV DNA usually detectable using standard determinations) or those who currently do not replicate HBV or replicate at low levels, routinely undetectable. HD subjects are in good position in diagnosis of HBV infection because they undergo periodic examinations of basic serologic HBV markers on a mandatory basis. However, it is also possible that HBV-infected patients with occult hepatitis B may be negative

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Table 5. Comparison of the distribution of *MCP1* rs1024611 polymorphic variants in HBsAg positive/anti-HBs negative HD patients and anti-HBc positive/HBsAg negative/anti-HBs positive HD without or with DM.

Genotype	HD patients HBsAg positive/ anti-HBs negative (frequency)	HD patients anti-HBc positive/ HBsAg negative/ anti-HBs positive HD (frequency)	Odds ratio (95%CI)	Two-tailed P	P_{trend}	$P_{genotyping}$	Power (%)
All HD patients							
	n=15	**n=126**					
AA	4 (0.27)	66 (0.52)	Referent	–	**0.021**	0.064	
AG	7 (0.47)	48 (0.38)	0.416 (0.085–1.756)	0.292			20.2
GG	4 (0.27)	12 (0.10)	0.182 (0.030–1.147)	0.073			56.3
AG+GG	11 (0.73)	60 (0.48)	0.331 (0.073–1.201)	0.105			38.4
MAF	15 (0.50)	72 (0.29)	0.400 (0.173–0.932)	**0.033**			61.4
HD cases without DM							
	n=10	**n=89**					
AA	3 (0.3)	49 (0.55)	Referent	–	**0.043**	0.096	
AG	4 (0.4)	32 (0.36)	0.490 (0.068–3.130)	0.602			11.9
GG	3 (0.3)	8 (0.09)	0.163 (0.019–1.494)	0.121			47.9
AG+GG	7 (0.7)	40 (0.45)	0.350 (0.055–1.672)	0.242			28.9
MAF	10 (0.5)	48 (0.27)	0.369 (0.130–1.062)	0.066			51.2
HD cases with DM							
	n=5	**n=37**					
AA	1 (0.2)	17 (0.46)	Referent	–	0.273	0.528	
AG	3 (0.6)	16 (0.43)	0.314 (0.006–4.509)	0.646			10.1
GG	1 (0.2)	4 (0.11)	0.235 (0.003–23.05)	0.791			10.4
AG+GG	4 (0.8)	20 (0.54)	0.294 (0.006–3.444)	0.550			6.9
MAF	5 (0.5)	24 (0.32)	0.480 (0.101–2.323)	0.451			15.9

anti-HBc – antibodies to core antigen of hepatitis B virus; anti-HBs – antibodies to surface antigen of hepatitis B virus; DM – diabetes mellitus, hemodialysis; HBsAg – surface antigen of hepatitis B virus; HD – hemodialysis; MAF – minor allele frequency.
Significant differences are indicated using bold font.

for all serological markers of HBV infection except HBV DNA [25]; this indicates a tremendous variability in chronic immunological reactions to HBV transmission. Our main purpose was to examine the possible association of *MCP1*-2518 A/G (rs1024611) polymorphism with anti-HBs development. Patients stratified by anti-HBs status represented different serological constellations, especially anti-HBc-positive/anti-HBs-negative subjects. Therefore, the anti-HBs-sorted groups were also analyzed by HBsAg status.

Comparison of *MCP1*-2518 A/G (rs1024611) polymorphic variant frequency between anti-HBc-positive HD patients and

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Table 6. Comparison of MCP1 rs1024611 genotype frequencies between hepatitis B virus carriers [AA 4 (0.27), AG 7 (0.47), GG 4 (0.27), MAF (0.50)] and other selected groups.

Description of HD group	rs1024611	rs1024611 genotype frequencies		Odds ratio (95%CI)	Two-tailed P	P_{trend}	$P_{genotyping}$	Power (%)
Controls (n=437)	AA	225	(0.51)	2.919 (0.846–12.73)	0.101	**0.010**	**0.021**	42.0
	AG	177	(0.41)	0.778 (0.242–2.571)	0.822			5.3
	GG	35	(0.08)	0.239 (0.067–1.091)	0.065			56.8
	AG+GG	212	(0.49)	0.343 (0.079–1.181)	0.101			41.9
	MAF	247	(0.28)	0.394 (0.177–0.880)	**0.022**			67.7
HD anti-HBc negative patients (n=754)	AA	349	(0.46)	2.370 (0.694–10.29)	0.209	**0.015**	**0.012**	26.9
	AG	352	(0.47)	1.001 (0.314–3.277)	1.000			3.6
	GG	53	(0.07)	0.208 (0.059–0.929)	**0.040**			61.4
	AG+GG	405	(0.54)	0.422 (0.097–1.442)	0.209			26.9
	MAF	458	(0.30)	0.436 (0.197–0.967)	**0.041**			59.5
HD patients with isolated anti-HBc positivity (n=28)	AA	16	(0.57)	3.667 (0.797–19.27)	0.110	**0.014**	**0.038**	39.0
	AG	11	(0.39)	0.740 (0.175–3.184)	0.882			5.0
	GG	1	(0.04)	0.102 (0.002–1.248)	0.086			60.3
	AG+GG	12	(0.43)	0.273 (0.052–1.254)	0.110			38.9
	MAF	13	(0.23)	0.302 (0.106–0.866)	**0.023**			66.8

anti-HBc – antibodies to core antigen of hepatitis B virus; HD – hemodialysis; MAF – minor allele frequency. Significant differences are indicated using bold font.

healthy controls indicate no association between *MCP1* genotypes and susceptibility to HBV infection, or anti-HBs development in HD patients already infected. Comparisons performed inside the entire anti-HBc-positive HD group also did not reveal any associations between *MCP1* genotypes and anti-HBs development in response to HBV infection. This lack of association was also evident in analyses in which DM and non-DM patients were analyzed separately. Associations of *MCP1* polymorphism with type 2 DM have been demonstrated [26,27], but in our studies there were no differences in *MCP1* genotype frequencies between type 2 DM subjects with diabetic nephropathy as a cause of ESRD and HD treatment, healthy controls, anti-HBc-negative HD patients [21], or anti-HBc-positive HD subjects (Supplementary Table 7). On the other hand, DM is a well-known predictor of hypo- or non-responsiveness to hepatitis B vaccination in patients with chronic renal diseases [28]. Therefore, DM could also influence anti-HBs production in response to HBV infection. However, the distribution of *MCP1* polymorphic variants was not associated with development of protective anti-HBs in response to hepatitis B vaccination, in DM as well as non-DM HD subjects not infected with HBV [21]. In the present study, the lack of *MCP1*-2518 A/G association with anti-HBs development was extended to HBV-infected HD patients with or without type 2 DM.

Stimulations with HBsAg and different fusion proteins eliciting moderate or high MCP-1 levels [with concomitant differences in tumor necrosis factor α (TNF-α), interleukin (IL)-12, IL-10, interferon-γ, and IL-6)] did not result in a significant difference in anti-HBs levels in transgenic mice [4], and reductions in serum and liver HBsAg levels were dependent on stimulation. High level productions of TNF-α and MCP-1 caused a more severe cytotoxicity in hepatocytes and were less effective in reducing serum HBsAg level. Studies by Meng et al. [4], although not exclusively related to MCP-1, clearly demonstrate that differences in MCP-1 concentrations do not correlate with anti-HBs levels but may be important for HBsAg clearance. It has been suggested that the anti-HBs response alone cannot account for the reduction of HBsAg [4], although anti-HBs appearance in the bloodstream is usually associated with HBsAg clearance. Therefore, a lack of association between *MCP1*-2518 A/G and anti-HBs development may not preclude the association between MCP1 and HBV clearance indicated by HBsAg disappearance from the blood.

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Supplementary Table 1. The distribution of *MCP1* rs1024611 genotypes in anti-HBc positive HD patients in respect to HWE.

MCP1 rs1024611 genotype frequencies	All HD cases		HD cases without DM		HD cases with DM	
	Observed	Expected	Observed	expected	Observed	expected
All anti-HBc positive HD patients (n=170)						
AA	87 (0.51)	85 (0.50)	66 (0.54)	63 (0.52)	21 (0.44)	21 (0.44)
AG	66 (0.39)	70 (0.41)	44 (0.36)	49 (0.40)	22 (0.46)	21 (0.44)
GG	17 (0.10)	15 (0.09)	12 (0.10)	10 (0.08)	5 (0.10)	6 (0.12)
P value for deviation from HWE	0.397		0.256		0.829	
Anti-HBs positive patients (n=127)						
AA	67 (0.53)	65 (0.51)	50 (0.56)	48 (0.53)	17 (0.46)	17 (0.46)
AG	48 (0.38)	52 (0.41)	32 (0.35)	35 (0.39)	16 (0.43)	16 (0.43)
GG	12 (0.09)	10 (0.08)	8 (0.09)	7 (0.08)	4 (0.11)	4 (0.11)
P value for deviation from HWE	0.433		0.388		0.935	
Anti-HBs negative patients (n=43)						
AA	20 (0.46)	19 (0.44)	16 (0.50)	15 (0.47)	4 (0.35)	5 (0.45)
AG	18 (0.42)	19 (0.44)	12 (0.38)	14 (0.44)	6 (0.55)	5 (0.45)
GG	5 (0.12)	5 (0.12)	4 (0.12)	3 (0.09)	1 (0.10)	1 (0.10)
P value for deviation from HWE	0.759		0.472		0.554	

anti-HBc – antibodies to core antigen of hepatitis B virus; anti-HBs – antibodies to surface antigen of hepatitis B virus; DM – diabetes mellitus; HD – hemodialysis; HWE – Hardy-Weinberg equilibrium.

Differences in *MCP1*-2518 A/G genotype frequencies are reflected in variations of MCP-1 blood concentrations [11,13–16]. In accordance with the available data, the involvement of *MCP1*-2518 A/G polymorphism in the outcome of HBV infection is, however, controversial [18,19]. To approach this problem, our further analyses on anti-HBc-positive HD patients were focused not only on anti-HBs status, but also on coexistence of HBsAg positivity and anti-HBs negativity, as well as the HBsAg negativity and anti-HBs positivity that represent serological profiles of HBV carrier status and recovery from HBV infection, respectively. For such analyses, patients with isolated anti-HBc positivity were excluded from the group of anti-HBc-positive/anti-HBs-negative subjects, as well as a unique HBsAg-positive/anti-HBs-positive patient was excluded from the group of anti-HBc-positive/anti-HBs-positive subjects. As a result, it became possible to show that the *MCP1*-2518G allele predisposes to maintenance of HBV infection (HBV carrier status). Therefore, our results support Korean findings indicating associations of *MCP1*-2518 A/G polymorphism with resolution/persistence of HBV infection (renal function in the examined subjects was not shown).

A weak point of this study is the small number of HBsAg-positive patients (HBV carriers). In the Greater Poland region of our country, the prevalence of HD patients infected with blood-borne viruses decreases every year due to rigorous sanitary regimen in dialysis facilities, and full implementation of hepatitis B vaccination in dialysis patients and medical staff. We consider this part of our study as preliminary field research, although it appears to be the first study on the association of *MCP1*-2518 A/G polymorphism with serological markers of HBV infection in HD patients.

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Supplementary Table 2. Comparison of the distribution of *MCP1* rs1024611 polymorphic variants in anti-HBc negative and anti-HBc positive HD without or with DM.

Genotype	HD patients anti-HBc negative (frequency)	HD patients anti-HBc positive (frequency)	Odds ratio (95%CI)	Two-tailed P	P_{trend}	$P_{genotyping}$	Power (%)
All HD patients							
	n=754	**n=170**					
AA	349 (0.46)	87 (0.51)	Referent	–	0.718	0.122	
AG	352 (0.47)	66 (0.39)	0.752 (0.520–1.086)	0.134			35.0
GG	53 (0.07)	17 (0.10)	1.287 (0.664–2.392)	0.493			12.0
AG+GG	405 (0.54)	83 (0.49)	0.822 (0.581–1.163)	0.285			19.4
MAF	458 (0.30)	100 (0.29)	0.955 (0.730–1.244)	0.781			5.6
HD cases without DM							
	n=532	**n=122**					
AA	245 (0.46)	66 (0.54)	Referent	–	0.493	**0.038**	
AG	255 (0.48)	44 (0.36)	0.641 (0.410–0.994)	0.047			53.6
GG	32 (0.06)	12 (0.10)	1.392 (0.617–2.961)	0.468			13.4
AG+GG	287 (0.54)	56 (0.46)	0.724 (0.478–1.096)	0.133			34.3
MAF	319 (0.30)	68 (0.28)	0.902 (0.652–1.240)	0.569			9.0
HD cases with DM							
	n=222	**n=48**					
AA	104 (0.47)	21 (0.44)	Referent	–	0.696	0.923	
AG	97 (0.44)	22 (0.46)	1.123 (0.550–2.296)	0.858			5.6
GG	21 (0.09)	5 (0.10)	1.179 (0.312–3.721)	0.956			5.2
AG+GG	118 (0.53)	27 (0.56)	1.133 (0.603–2.245)	0.820			5.2
MAF	139 (0.31)	32 (0.33)	1.097 (0.662–1.791)	0.783			6.0

anti-HBc – antibodies to core antigen of hepatitis B virus; DM – diabetes mellitus, hemodialysis; HD – hemodialysis; MAF – minor allele frequency. Significant differences are indicated using bold font.

Conclusions

In this study we have demonstrated that *MCP1*-2518 A/G (rs1024611) polymorphism is not associated with anti-HBs development in response to hepatitis B infection in HD patients, independent of whether they are type 2 diabetics. In our previous study on HD patients [21], we documented that this polymorphism is also not associated with response to hepatitis B vaccination characterized by seroconversion to anti-HBs >10 U/L. However, the role of *MCP1*-2518 A/G polymorphism in the HBsAg clearance may be seen from our current studies, and seems to be worth further investigation, especially in immunocompromised patients.

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Supplementary Table 3. Comparison of the distribution of *MCP1* rs1024611 polymorphic variants in anti-HBs-positive HD due to vaccination or infection

Genotype	Anti-HBs positive HD patients due to vaccination (frequency)	Anti-HBs positive HD patients due to infection (frequency)	Odds ratio (95%CI)	Two-tailed P	P_{trend}	$P_{genotyping}$	Power (%)
All HD patients							
	n=601	**n=127**					
AA	284 (0.47)	67 (0.53)	Referent	–	0.693	0.143	
AG	279 (0.46)	48 (0.38)	0.729 (0.475–1.115)	0.153			30.1
GG	38 (0.07)	12 (0.09)	1.339 (0.603–2.790)	0.520			12.0
AG+GG	317 (0.53)	60 (0.47)	0.802 (0.536–1.199)	0.303			18.1
MAF	355 (0.29)	72 (0.28)	0.944 (0.689–1.284)	0.768			6.0
HD cases without DM							
	n=426	**n=90**					
AA	201 (0.47)	50 (0.56)	Referent	–	0.505	0.073	
AG	203 (0.48)	32 (0.36)	0.634 (0.377–1.055)	0.082			41.6
GG	22 (0.05)	8 (0.09)	1.462 (0.530–3.659)	0.518			13.1
AG+GG	225 (0.53)	40 (0.44)	0.715 (0.440–1.157)	0.184			29.8
MAF	247 (0.29)	48 (0.27)	0.891 (0.606–1.293)	0.596			8.6
HD cases with DM							
	n=175	**n=37**					
AA	83 (0.47)	17 (0.46)	Referent	–	0.789	0.949	
AG	76 (0.43)	16 (0.43)	1.028 (0.451–2.334)	1.000			3.5
GG	16 (0.09)	4 (0.11)	1.221 (0.264–4.460)	0.961			5.2
AG+GG	92 (0.53)	20 (0.54)	1.061 (0.491–2.316)	1.000			4.8
MAF	108 (0.31)	24 (0.32)	1.076 (0.600–1.889)	0.890			5.1

anti-HBs – antibodies to surface antigen of hepatitis B virus; DM – diabetes mellitus; MAF – minor allele frequency.

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Supplementary Table 4. Comparison of the distribution of *MCP1* rs1024611 polymorphic variants in anti-HBs-negative hemodialysis (HD) patients despite vaccination or infection.

Genotype	Anti-HBs negative HD patients despite vaccination (frequency)	Anti-HBs negative HD patients despite infection (frequency)	Odds ratio (95%CI)	Two-tailed P	P_{trend}	$P_{genotyping}$	Power (%)
All HD patients							
	n=153	**n=43**					
AA	65 (0.42)	20 (0.47)	Referent	–	0.845	0.786	
AG	73 (0.48)	18 (0.42)	0.801 (0.365–1.752)	0.674			8.4
GG	15 (0.10)	5 (0.11)	1.083 (0.273–3.662)	1.000			4.0
AG+GG	88 (0.57)	23 (0.53)	0.849 (0.408–1.782)	0.764			5.9
MAF	103 (0.34)	28 (0.33)	0.952 (0.549–1.624)	0.957			4.4
HD cases without DM							
	n=106	**n=32**					
AA	44 (0.42)	16 (0.50)	Referent	–	0.680	0.511	
AG	52 (0.49)	12 (0.38)	0.635 (0.246–1.160)	0.402			13.7
GG	10 (0.09)	4 (0.13)	1.100 (0.220–4.536)	1.000			3.5
AG+GG	62 (0.58)	16 (0.50)	0.710 (0.297–1.699)	0.517			11.8
MAF	72 (0.34)	20 (0.31)	0.884 (0.478–1.666)	0.808			5.5
HD cases with DM							
	n=47	**n=11**					
AA	21 (0.45)	4 (0.36)	Referent	–	0.757	0.839	
AG	21 (0.45)	6 (0.55)	1.500 (0.301–8.269)	0.832			5.6
GG	5 (0.11)	1 (0.09)	1.050 (0.018–14.37)	1.000			1.9
AG+GG	26 (0.55)	7 (0.64)	1.413 (0.307–7.465)	0.879			6.3
MAF	31 (0.33)	8 (0.36)	1.161 (0.379–3.345)	0.945			4.9

anti-HBs – antibodies to surface antigen of hepatitis B virus; DM – diabetes mellitus; MAF – minor allele frequency.

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Supplementary Table 5. Comparison of the distribution of *MCP1* rs1024611 polymorphic variants between HD patients with isolated anti-HBc positivity and HD patients with HBV resolution.

Genotype	HD patients with isolated anti-HBc positivity (frequency)	HD patients anti-HBc positive/ HBsAg negative/ anti-HBs positive HD (frequency)	Odds ratio (95%CI)	Two-tailed P	P_{trend}	$P_{genotyping}$	Power (%)
All HD patients							
	n=28	n=126					
AA	16 (0.57)	66 (0.52)	Referent	–	0.427	0.586	
AG	11 (0.39)	48 (0.38)	1.058 (0.417–2.765)	1.000			3.8
GG	1 (0.04)	12 (0.10)	2.909 (0.373–132.0)	0.550			2.6
AG+GG	12 (0.43)	60 (0.48)	1.212 (0.492–3.052)	0.807			5.4
MAF	13 (0.23)	72 (0.29)	1.323 (0.650–2.844)	0.525			10.1

anti-HBc – antibodies to core antigen of hepatitis B virus; HBV – hepatitis B virus; HD – hemodialysis.

Supplementary Table 6. Distribution of main demographic and clinical data in the entire group of anti-HBc positive hemodialysis patients selected according to genotypes of *MCP1* rs1024611.

Parameter	AA n=87	AG n=66	GG n=17	P value between all groups
Male gender (n,%)	53 (60.9)	34 (51.5)	12 (70.6)	0.290[a]
Age (years)	61.1±14.7	62.7±14.3	61.4±16.8	0.979[b]
Diabetic nephropathy (n,%)	21 (24.1)	22 (33.3)	5 (29.4)	0.462[a]
Chronic glomerulonephritis (n,%)	16 (18.4)	12 (18.2)	4 (23.5)	0.917[a]
Hypertensive nephropathy (n,%)	18 (20.7)	8 (12.1)	0 (0.0)	0.066[c]
Chronic tubulointerstitial nephritis (n,%)	5 (5.7)	5 (7.6)	3 (17.6)	0.237[a]
Polycystic kidney disease (n,%)	4 (4.6)	4 (6.1)	0 (0.0)	0.766[c]
RRT vintage (years)	2.5 (0.05–25.1)	3.6 (0.05–26.3)	2.3 (0.14–24.8)	0.512[d]
HBsAg positive/anti-HBs negative (n,%)	4 (4.6)	7 (10.6)	4 (23.5)	**0.028**[a] AA *vs.* AG p=0.268[e] **AA *vs.* GG p=0.029**[e] AG *vs.* GG p=0.317[e]
HBsAg negative/anti-HBs positive (n,%)	66 (75.9)	48 (72.7)	12 (70.6)	0.844[a]
Isolated anti-HBc positivity (n,%)	16 (18.4)	11 (16.7)	1 (5.9)	0.472[a]
HBsAg positive/anti-HBs positive (n,%)	1 (1.1)	0 (0.0)	0 (0.0)	1.000[c]
ALT (U/L)	17 (3–50)	15 (2–195)	19 (9–95)	0.266[d]
AST (U/L)	16 (6–72)	19 (9–152)	18 (9–64)	0.571[d]
GGT (U/L)	25 (4–498)	27 (5–211)	35 (10–147)	0.757[d]

ALT – alanine aminotransferase; anti-HBc – antibodies to core antigen of hepatitis B virus; anti-HBs – antibodies to surface antigen of hepatitis B virus; AST – aspartate aminotransferase; GGT – gamma-glutamyltranspeptidase; HBsAg – surface antigen of hepatitis B virus; RRT – renal replacement therapy. Statistical tests: a – Chi square; b – ANOVA; c – Fisher Freeman Halton; d – Kruskal-Wallis; e – Yates corrected Chi-square. Significant differences are indicated using bold font.

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Supplementary Table 7. Comparison of the distribution of *MCP1* rs1024611 polymorphic variants in all anti-HBc positive HD patients as well as in non-DM and DM patients to respective genotype frequencies in controls.

Genotype	HD patients (frequency)	Controls (frequency)	Odds ratio (95%CI)	Two-tailed P	P_{trend}	$P_{genotyping}$	Power (%)
All HD patients							
	n=170	**n=437**					
AA	87 (0.51)	225 (0.51)	Referent	–	0.693	0.721	
AG	66 (0.39)	177 (0.41)	0.964 (0.650–1.428)	0.927			4.8
GG	17 (0.10)	35 (0.08)	1.256 (0.625–2.443)	0.578			10.1
AG+GG	83 (0.49)	212 (0.49)	1.013 (0.699–1.466)	1.000			4.7
MAF	100 (0.29)	247 (0.28)	1.058 (0.793–1.405)	0.740			6.5
HD cases without DM							
	n=122	**n=437**					
AA	66 (0.54)	225 (0.51)	Referent	–	0.905	0.613	
AG	44 (0.36)	177 (0.41)	0.848 (0.537–1.329)	0.519			10.2
GG	12 (0.10)	35 (0.08)	1.169 (0.522–2.466)	0.790			6.6
AG+GG	56 (0.46)	212 (0.49)	0.901 (0.589–1.373)	0.684			6.7
MAF	68 (0.28)	247 (0.28)	0.981 (0.703–1.358)	0.973			4.6
HD cases with DM							
	n=48	**n=437**					
AA	21 (0.44)	225 (0.51)	Referent	–	0.297	0.573	
AG	22 (0.46)	177 (0.41)	1.332 (0.674–2.634)	0.463			12.0
GG	5 (0.10)	35 (0.08)	1.531 (0.423–4.538)	0.579			11.7
AG+GG	27 (0.56)	212 (0.49)	1.365 (0.718–2.621)	0.387			17.0
MAF	32 (0.33)	247 (0.28)	1.269 (0.782–2.025)	0.355			17.1

anti-HBc – antibodies to core antigen of hepatitis B virus; DM – diabetes mellitus, hemodialysis; HD – hemodialysis; MAF – minor allele frequency.

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Conflict of interest

None declared.

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