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INTRODUCTION

Monocyte chemoattractant protein 1 (MCP-1) is involved in the pathogenesis of renal diseases, diabetes, and hepatitis B virus (HBV) clearance.

OBJECTIVES

The aim of the study was to evaluate the distribution of MCP1 –2518 A/G (rs1024611) polymorphic variants in patients on hemodialysis (HD) with respect to their responsiveness to hepatitis B vaccination.

PATIENTS AND METHODS

Patients on HD, never infected with HBV, were enrolled into the study after receiving an appropriate hepatitis B vaccine. The HD group consisted of 601 individuals who responded to vaccination with anti-HBs titer exceeding 10 IU/l considered as protective and 153 nonresponders, in whom no adequate response was observed (anti-HBs, ≤10 IU/l). There were 175 diabetic patients among responders and 47 diabetic patients among nonresponders. Healthy subjects served as controls (n = 437).

MCP1 genotyping was determined by polymerase chain reaction–restriction fragment length polymorphism.

RESULTS

The distribution of MCP1 rs1024611 polymorphic variants in controls was as follows: AA, 51%; AG, 41%; GG, 8%. There were no significant differences (P >0.05) in MCP1 distribution between the study groups and controls, independently of the occurrence of diabetes and responsiveness to hepatitis B vaccination. HD groups that were identified based on diabetic status and responsiveness to hepatitis B vaccination did not differ in MCP1 distribution.

CONCLUSIONS

MCP1-2518 A/G polymorphism is not associated with responsiveness to hepatitis B vaccination in patients on HD, independently of whether they have diabetes or not.

KEY WORDS

diabetes, hemodialysis, hepatitis B vaccination, MCP1 –2518 A/G rs1024611, monocyte chemoattractant protein 1
of carpal tunnel syndrome. A significant difference in MCP1 –2518 A>G genotype frequencies between the entire group of HD patients and controls was also demonstrated, because allele G carriers occurred in this study significantly more often in patients with cardiovascular diseases (CVD), who constituted 63% of the group. There was no statistically significant difference in the distribution of MCP1 genotypes between HD patients without CVD and healthy controls. In the study by Park et al. on Korean subjects, the promoter polymorphism of MCP1 (MCP1 –2518G>A) was involved in HBV clearance, which is associated with the development of antibodies to surface antigen of HBV (anti-HBs): the frequency of homozygotes for the MCP1 –2518A allele among chronic HBV carriers was significantly higher than that among spontaneously recovered subjects. However, a year later, Cheong et al. did not demonstrate an association of MCP1 –2518G>A with the outcome of HBV infection in Korean patients.

As shown in the Multicenter Polish Population Health Status Study (WOBASZ), the incidence of diabetes in Poland is 6.8%. Diabetes is the most common cause of end-stage renal disease (ESRD) in many HD settings. The association of the MCP1 polymorphism with diabetes was demonstrated. Diabetes was also recognized as a cause of hypo- or nonresponsiveness to hepatitis B vaccination in patients on renal replacement therapy (RRT). However, in the available literature, we have not found associations between the MCP1 polymorphism in diabetes and responsiveness to hepatitis B vaccination in HD patients.

Our aim was to evaluate distribution of MCP1 –2518 A/G (rs1024611) polymorphic variants in HD patients with respect to their responsiveness to hepatitis B vaccination. The effect of MCP1 –2518 A/G genotypes on response to hepatitis B vaccination was also investigated in type 2 diabetes as the cause of diabetic nephropathy and ESRD.

**PATIENTS AND METHODS**

**Patients and controls** Unrelated HD patients were enrolled into the study if they 1) were never infected with HBV as indicated by medical history and results of HBV seromarkers: both surface antigen of HBV (HBsAg) and antibodies to core antigen of HBV (anti-HBc) were negative; 2) underwent full vaccination series against HBV that is recommended for HD patients (4 doses of 40 µg each at 0, 1, 2, 6 months) and developed anti-HBs titers considered as protective (>10 IU/l) in response to this primary vaccination or additional vaccine doses; 3) received full vaccination series against HBV that is recommended for HD patients and at least 3 additional vaccine doses and did not develop protective anti-HBs titer.

Patients were hepatitis-B vaccinated with recombinant DNA yeast-derived vaccines, composed of the S protein of HBsAg (Engerix B, Glaxo-SmithKline Biologicals, Belgium; Hepavax–Gene, BIOMED SA, Poland; Euvax B, LG Life Sciences Ltd., South Korea).

HD patients with carpal tunnel syndrome or active tuberculosis or both were excluded from the study. CVD was not the inclusion criterion because diastolic cardiac dysfunction occurs in 93% of HD patients and progresses in the course of HD therapy. Therefore, near all HD patients have more or less pronounced cardiac damage.

The entire HD group consisted of 754 patients. Type 2 diabetes was diagnosed in 222 patients (29.4%), and diabetes was a cause of diabetic nephropathy and ESRD in all those patients. There were no patients with type 1 diabetes. There were 601 hepatitis-B-vaccine responders (79.7%) and 153 nonresponders (20.3%). In the nondiabetic group (n = 532), there were 426 responders (80.1%); in the diabetic group (n = 222), there were 106 responders (47.7%). A difference in the prevalence of responders in nondiabetic and diabetic groups was significant (P < 0.0001). Selected demographic and clinical data of the main groups of HD patients are shown in Table 1.

Unrelated blood donors and healthy volunteers from the same geographical area served as controls (n = 437). This control group was also used in the earlier study for comparison of MCP1 –2518 A>G (rs1024611) polymorphic variants in patients suffering from primary glomerulonephritis and healthy individuals.

All examined subjects were Caucasians.

**Genotyping** MCP1 rs1024611 genotyping was determined by polymerase chain reaction–restriction fragment length polymorphism as previously described.

**Statistical methods** Descriptive statistics 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. The χ² test or Mann–Whitney test was used for the comparison of data obtained in selected groups of HD patients, as appropriate.

The Hardy–Weinberg equilibrium (HWE) was tested to compare the observed genotype frequencies to the expected ones using the χ² test with 1 degree of freedom. In all HD responders as well as in nondiabetic HD responders, there was a deviation from the HWE in the observed MCP1 genotype frequencies compared with the expected ones (Supplementary material online, Table S1). The Fisher exact test or χ² test was used to evaluate differences in genotype and allele prevalence between the study groups. The odds ratio and 95% confidence interval (95% CI) were also calculated and adjusted for sex, age, duration of RRT, and chronic glomerulonephritis, as appropriate. Polymorphisms were tested for association using the χ² test for trend (P trend). Power analysis was performed by the uncorrected χ² test available at an online internet service.
RESULTS HD patients (n = 754), nondiabetics (n = 532), and diabetics (n = 222) did not differ in MCP1 genotype frequencies from controls (Supplementary material online, Table S2). The frequency of distribution of MCP1 polymorphic variants was also nonsignificant between all diabetic and all nondiabetic subjects (Supplementary material online, Table S3).

The distribution of the main demographic and clinical variables between responders (n = 601) and nonresponders (n = 153) is shown in Table 1. Responders to hepatitis B vaccination (n = 601) did not differ from nonresponders to hepatitis B vaccination (n = 153) in terms of demographic and clinical variables (Table 2).

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

**RESULTS** HD patients (n = 754), nondiabetic patients (n = 532), and diabetic patients (n = 222) did not differ in MCP1 genotype frequencies from controls (Supplementary material online, Table S2). The frequency of distribution of MCP1 polymorphic variants was also nonsignificant between all diabetic and all nondiabetic subjects (Supplementary material online, Table S3). The distribution of the main demographic and clinical variables between responders (n = 601) and nonresponders (n = 153) is shown in Table 1. Responders to hepatitis B vaccination (n = 601) did not differ from nonresponders to hepatitis B vaccination (n = 153) in terms of demographic and clinical variables (Table 2).

**TABLE 1** Selected demographic and clinical data of the main groups of patients on hemodialysis

| All HD patients (n = 754) | responders (n = 601) | nonresponders (n = 153) | P value |
|--------------------------|----------------------|-------------------------|---------|
| men, n (% of all)        | 360 (59.9)           | 79 (51.6)               | 0.064*  |
| age, y                   | 61.7 ± 15.1          | 66.9 ± 14.4             | <0.001† |
| RRT duration, y          | 2.6 (0.003–26.1)     | 1.1 (0.03–11.6)         | <0.001† |
| causes of end-stage renal disease, n (% of all) |                      |                        |         |
| diabetic nephropathy     | 175 (29.1)           | 47 (30.7)               | 0.766*  |
| hypertensive nephropathy | 118 (19.6)           | 29 (19.0)               | 0.909*  |
| chronic glomerulonephritis | 93 (15.5)          | 9 (5.8)                 | 0.002*  |
| chronic tubulointerstitial nephritis | 57 (9.5)        | 19 (12.4)               | 0.293*  |
| polycystic kidney disease | 43 (7.2)            | 5 (3.2)                 | 0.094*  |
| 3461c, 1752c, 3691c, 1884c, or other | 115 (19.1)        | 44 (28.8)               | 0.011†  |

**TABLE 2** Selected demographic and clinical data of responders and nonresponders to hepatitis B vaccination

| parameters to hepatitis B vaccination (n = 601) | diabetics (n = 175) | nondiabetics (n = 426) | P value |
|-------------------------------------------------|---------------------|------------------------|---------|
| men, n (% of all)                               | 103 (58.9)          | 257 (60.3)             | 0.784*  |
| age, y                                          | 65.8 ± 12.8         | 60.0 ± 15.7            | <0.001† |
| RRT duration, y                                 | 2.6 (0.09–18.3)     | 2.6 (0.003–26.1)       | 0.064*  |
| causes of end-stage renal disease, n (% of all) |                      |                        |         |
| diabetic nephropathy                            | 175 (100)           | 0 (0)                  |         |
| chronic glomerulonephritis                      | –                   | 93 (21.8)              |         |
| hypertensive nephropathy                        | –                   | 118 (27.7)             |         |
| chronic tubulointerstitial nephritis            | –                   | 57 (13.4)              |         |
| polycystic kidney disease                       | –                   | 42 (9.9)               |         |
| 3461c, 1752c, 3691c, 1884c, or other            | –                   | 116 (27.2)             |         |

| parameters to hepatitis B vaccination (n = 153) | diabetics (n = 47) | nondiabetics (n = 106) | P value |
|-------------------------------------------------|---------------------|------------------------|---------|
| men, n (% of all)                               | 24 (51.1)           | 55 (51.9)              | 1.000*  |
| age, y                                          | 68.2 ± 13.5         | 66.3 ± 14.8            | 0.442*  |
| RRT duration, y                                 | 1.0 (0.09–8.2)      | 1.2 (0.03–11.6)        | 0.373*  |
| causes of end-stage renal disease, n (% of all) |                      |                        |         |
| diabetic nephropathy                            | 47 (100)            | 0 (0)                  |         |
| chronic glomerulonephritis                      | –                   | 9 (8.5)                |         |
| hypertensive nephropathy                        | –                   | 29 (27.4)              |         |
| chronic tubulointerstitial nephritis            | –                   | 19 (17.9)              |         |
| polycystic kidney disease                       | –                   | 5 (4.7)                |         |
| 1752c, 2578c, 1832c, 1396c, or other            | –                   | 44 (41.5)              |         |

a Chi-squared test  
b Mann–Whitney test  
c Renal diagnosis codes for the ERA-EDTA

Abbreviations: HD – hemodialysis, RRT – renal replacement therapy

A P value of less than 0.05 was considered statistically significant. All probabilities were 2-tailed. Statistical calculations were performed using GraphPad InStat 3.06, 32-bit for Windows, created September 5, 2003 (GraphPad Software, Inc., La Jolla, California, United States), CytelStudio Version 9.0, created March 17, 2010 (CytelStudio Software Corporation, Cambridge, United States), and Statistica Version 10, 2011 (Stat Soft, Inc., Tulsa, Oklahoma, United States).
Clinical data in the entire group of HD patients (n = 754) selected according to the genotypes of MCP1 rs1024611 did not show statistical differences (Supplementary material online, Table S4).

Classification of HD patients (all subjects, diabetic, nondiabetic) into responders and nonresponders to hepatitis B vaccine did not reveal differences in the distribution of the respective genotypes and allele frequencies of MCP1 rs1024611 between all HD groups and controls (Table 2) as well as between all HD groups (Tables 4-6). However, a borderline significance was demonstrated between all HD nonresponders and controls as well as nondiabetic HD nonresponders and controls (Table 3). To clarify this trend, the genotype analysis was repeated with the exclusion of 20 patients in whom causes of ESRD included severe immune-compromise diseases (multiple myeloma, 7 cases; amyloidosis, 4 cases; antineutrophil cytoplasmic antibodies-related vasculitis, 4 cases; lupus nephritis, 3 cases; renal/urinary tract cancer, 2 cases). To treat those diseases, appropriate medications including corticosteroids and immunosuppressants were used. HD patients who entered the final analysis (n = 133) did not show any differences in the distribution of MCP1 rs1024611 genotypes, while a small group of severely immunocompromised HD patients (n = 20) demonstrated a borderline difference in MCP1 polymorphism compared with controls (Supplementary material online, Table S5).

**DISCUSSION**

In the past decade, the association of immune response to hepatitis B vaccination with genotypes of cytokines, their receptors, and toll-like receptors (IL1A, IL1RA, IL1B, IL2, IL4, IL6, IL10, IL10RA, IL12A, IL12B, IL15, IL18, MAPK (JNK1), TLR3, TNF-α) was intensively studied with different results.²⁹⁻⁴⁶ In this study, we focused on the polymorphic variants of MCP1.

Distribution of MCP1 -2518 G>A polymorphism varies significantly in published reports, even among healthy subjects.⁷⁻¹²,²¹⁻²⁶,⁴¹⁻⁴⁶ (Supplementary material online, Table S6). In uremic milieu, the immune system is compromised, but severity of its deterioration may differ between HD patients. An example of this variability is responsiveness to hepatitis B vaccination. Up to 20% of HD patients are nonresponders despite advanced compromise diseases (multiple myeloma, 7 cases; amyloidosis, 4 cases; antineutrophil cytoplasmic antibodies-related vasculitis, 4 cases; lupus nephritis, 3 cases; renal/urinary tract cancer, 2 cases). To treat those diseases, appropriate medications including corticosteroids and immunosuppressants were used. HD patients who entered the final analysis (n = 133) did not show any differences in the distribution of MCP1 rs1024611 genotypes, while a small group of severely immunocompromised HD patients (n = 20) demonstrated a borderline difference in MCP1 polymorphism compared with controls (Supplementary material online, Table S5).

### TABLE 1

| Genotype | Responders (frequency) | Controls (frequency) | Odds ratio (95% CI) | 2-tailed P | P_{trend} | P_{genotyping} | Power, % |
|----------|------------------------|----------------------|---------------------|------------|----------|---------------|----------|
| all HD cases vs. controls | | | | | | | |
| n = 601 | 284 (0.47) | 225 (0.51) | referent | – | 0.513 | 0.138 | – |
| AG | 279 (0.46) | 177 (0.41) | 1.249 (0.958–1.629) | 0.103 | – | – | 38.7 |
| GG | 38 (0.07) | 35 (0.08) | 0.860 (0.511–1.453) | 0.633 | – | – | 8.4 |
| AG+GG | 317 (0.53) | 212 (0.49) | 1.185 (0.919–1.528) | 0.199 | – | – | 25.4 |
| MAF | 355 (0.29) | 247 (0.28) | 1.064 (0.874–1.296) | 0.561 | – | – | 9.2 |

| HD cases without diabetes vs. controls | | | | | | | |
| n = 426 | 201 (0.47) | 225 (0.51) | referent | – | 0.727 | 0.051 | – |
| AG | 203 (0.48) | 177 (0.41) | 1.284 (0.964–1.710) | 0.089 | – | – | 42.6 |
| GG | 22 (0.05) | 35 (0.08) | 0.704 (0.380–1.281) | 0.280 | – | – | 21.0 |
| AG+GG | 225 (0.53) | 212 (0.49) | 1.188 (0.901–1.566) | 0.231 | – | – | 23.8 |
| MAF | 247 (0.29) | 247 (0.28) | 1.036 (0.836–1.284) | 0.778 | – | – | 6.0 |

| HD cases with diabetes vs. controls | | | | | | | |
| n = 175 | 83 (0.47) | 225 (0.51) | referent | – | 0.365 | 0.650 | – |
| AG | 76 (0.43) | 177 (0.41) | 1.164 (0.791–1.710) | 0.475 | – | – | 12.4 |
| GG | 16 (0.09) | 35 (0.08) | 1.239 (0.606–2.441) | 0.618 | – | – | 9.1 |
| AG+GG | 92 (0.53) | 212 (0.49) | 1.176 (0.815–1.698) | 0.413 | – | – | 14.6 |
| MAF | 108 (0.31) | 247 (0.28) | 1.133 (0.855–1.496) | 0.403 | – | – | 14.2 |

Abbreviations: CI = confidence interval, MAF = minor allele frequency, others – see Table 1

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**ORIGINAL ARTICLE** Polymorphism of monocyte chemoattractant protein 1 (MCP1 -2518 A/G)...
The current study showed that re...1.305 (0.933–1.816)
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1.502 (0.937–2.412)
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41.9
1.249 (0.765–2.004)
15 (0.10)
44 (0.42)
212 (0.49)
1.437 (0.975–2.122)
0.068
–
47.7
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HD cases without diabetes vs. controls
n = 106
n = 437
AA 44 (0.42) 225 (0.51) referent – 0.099 0.182 –
AG 52 (0.49) 177 (0.41) 1.502 (0.937–2.412) 0.093 – – 39.7
GG 10 (0.09) 35 (0.08) 1.461 (0.599–3.294) 0.444 – – 15.1
AG+GG 62 (0.58) 212 (0.49) 1.495 (0.953–2.358) 0.082 – – 41.6
MAF 72 (0.34) 247 (0.28) 1.305 (0.933–1.816) 0.123 – – 35.6
HD cases with diabetes vs. controls
n = 47
n = 437
AA 21 (0.45) 225 (0.51) referent – 0.337 0.630 –
AG 21 (0.46) 177 (0.41) 1.271 (0.638–2.531) 0.562 – – 10.1
GG 5 (0.11) 35 (0.08) 1.531 (0.423–4.538) 0.579 – – 11.7
AG+GG 26 (0.55) 212 (0.49) 1.314 (0.687–2.536) 0.463 – – 13.4
MAF 31 (0.33) 247 (0.28) 1.249 (0.765–2.004) 0.398 – – 15.0
Abbreviations: see TABLES 1 and 2

TABLE 3

| Genotype | Nonresponders (frequency) | Controls (frequency) | Odds ratio (95% CI) | 2-tailed P | P* trend | P* genotyping | Power, % |
|----------|---------------------------|---------------------|--------------------|-----------|----------|--------------|----------|
| all HD cases vs. controls |
| n = 153 | n = 437 |
| AA      | 65 (0.42) 225 (0.51) | referent             | –                  | 0.073     | 0.158    | –            |
| AG      | 73 (0.48) 177 (0.41) | 1.428 (0.951–2.145) | 0.089              | –         | 43.0     |
| GG      | 15 (0.10) 35 (0.08)  | 1.484 (0.706–2.992) | 0.323              | –         | 19.9     |
| AG+GG   | 88 (0.57) 212 (0.49) | 1.437 (0.975–2.122) | 0.068              | –         | 47.7     |
| MAF     | 103 (0.34) 247 (0.28) | 1.288 (0.963–1.717) | 0.089              | –         | 41.5     |
| HD cases without diabetes vs. controls |
| n = 106 | n = 437 |
| AA      | 44 (0.42) 225 (0.51) | referent             | –                  | 0.099     | 0.182    | –            |
| AG      | 52 (0.49) 177 (0.41) | 1.502 (0.937–2.412) | 0.093              | –         | –        | 39.7        |
| GG      | 10 (0.09) 35 (0.08)  | 1.461 (0.599–3.294) | 0.444              | –         | –        | 15.1        |
| AG+GG   | 62 (0.58) 212 (0.49) | 1.495 (0.953–2.358) | 0.082              | –         | –        | 41.6        |
| MAF     | 72 (0.34) 247 (0.28) | 1.305 (0.933–1.816) | 0.123              | –         | –        | 35.6        |
| HD cases with diabetes vs. controls |
| n = 47  | n = 437 |
| AA      | 21 (0.45) 225 (0.51) | referent             | –                  | 0.337     | 0.630    | –            |
| AG      | 21 (0.46) 177 (0.41) | 1.271 (0.638–2.531) | 0.562              | –         | –        | 10.1        |
| GG      | 5 (0.11) 35 (0.08)   | 1.531 (0.423–4.538) | 0.579              | –         | –        | 11.7        |
| AG+GG   | 26 (0.55) 212 (0.49) | 1.314 (0.687–2.536) | 0.463              | –         | –        | 13.4        |
| MAF     | 31 (0.33) 247 (0.28) | 1.249 (0.765–2.004) | 0.398              | –         | –        | 15.0        |

status, and also their genetic pattern associated with protective antibody generation may be typical of the majority of healthy subjects. Not surprisingly, HD patients with maintained responsiveness to hepatitis B vaccination did not differ significantly from controls with respect to the distribution of MCP1 −2518 G>A polymorphic variants, independently of the cause of ESRD (diabetic or nondiabetic). However, nonresponders had a similar distribution of MCP1 polymorphic variants to healthy subjects, which indicates that MCP1 polymorphism does not contribute significantly to the responsiveness to hepatitis B vaccination in HD patients, at least in those having primary renal diseases or type 2 diabetes as a cause of ESRD.

In the largest groups (all HD responders and nondiabetic HD responders), there was a deviation from the HWE in the observed MCP1 genotype frequencies compared with the expected ones. Such a lack of consistency with the HWE was also shown in the group of HD patients in the study by Buraczyńska et al.1 We can explain the deviation from the HWE by variability in the causes of ESRD and existence of comorbidities in both these groups. Associations of MCP1 polymorphic variants with many pathological conditions have been demonstrated, which are frequently present also in HD patients: CVD (including coronary artery disease, myocardial infarction, and ischemic stroke) carpal tunnel syndrome, HBV clearance, progression of renal disease in immunoglobulin A nephropathy, metabolic syndrome, and diabetes. On the other hand, there have also been studies that failed to show associations between MCP1 −2518 A/G and coronary artery disease or myocardial infarction. Recently, it has been suggested that the −2518 A/G polymorphism in MCP1 would be a risk factor for tuberculosis, HD patients in our study had no acute tuberculosis during the study period, but 4 responders had tuberculosis in the past. There have also been reports on associations of MCP1 polymorphism with lupus nephritis, psoriasis, and hypertension. Despite efforts to obtain a relatively homogeneous HD group, patients differed in the causes of ESRD, which may result in a deviation of their genotypes from the HWE, especially that a consistency with the HWE was shown for MCP1 polymorphic variants in healthy controls and diabetic HD group.

Diabetes is the main cause of ESRD requiring RRT. In the Hemodialysis (HEMO) Study, the group of HD patients comprised approximately 45% of diabetic subjects. In our previous study, among HD nonresponders to hepatitis B vaccination, the number of diabetic subjects was higher by over 12% compared with the group of responders. The current study showed that responsiveness to hepatitis B vaccination in the diabetic group was lower by 32.4% than that in...
### TABLE 4  Distribution of MCP1 rs1024611 polymorphic variants in hemodialyzed nonresponders and responders

| Genotype | Nonresponders (frequency) | Responders (frequency) | Odds ratio (95% CI) | 2-tailed $P$ | $P_{\text{trend}}$ | Power, % |
|----------|---------------------------|------------------------|---------------------|-------------|------------------|---------|
| all HD cases | n = 153 | n = 601 | | | | |
| AA | 65 (0.42) | 284 (0.47) | | | | |
| AG | 73 (0.48) | 279 (0.46) | 1.143 (0.774–1.690) | 0.543 | | |
| GG | 15 (0.10) | 38 (0.07) | 1.725 (0.828–3.437) | 0.151 | | |
| AG+GG | 88 (0.57) | 317 (0.53) | 1.213 (0.835–1.767) | 0.334 | | |
| MAF | 103 (0.34) | 355 (0.29) | 1.211 (0.916–1.593) | 0.184 | | |
| HD cases without diabetes | n = 106 | n = 426 | | | | |
| AA | 44 (0.42) | 201 (0.47) | | | | |
| AG | 52 (0.49) | 203 (0.48) | 1.170 (0.731–1.878) | 0.564 | | |
| GG | 10 (0.09) | 22 (0.05) | 2.076 (0.815–4.953) | 0.131 | | |
| AG+GG | 62 (0.58) | 225 (0.53) | 1.259 (0.801–1.988) | 0.347 | | |
| MAF | 72 (0.34) | 247 (0.29) | 1.260 (0.900–1.753) | 0.185 | | |
| HD cases with diabetes | n = 47 | n = 175 | | | | |
| AA | 21 (0.45) | 83 (0.47) | | | | |
| AG | 21 (0.45) | 76 (0.43) | 1.092 (0.522–2.285) | 0.935 | | |
| GG | 5 (0.11) | 16 (0.09) | 1.235 (0.317–4.073) | 0.907 | | |
| AG+GG | 26 (0.55) | 92 (0.53) | 1.117 (0.557–2.258) | 0.866 | | |
| MAF | 31 (0.33) | 108 (0.31) | 1.103 (0.653–1.834) | 0.782 | | |

*adjusted for sex, age, duration of renal replacement therapy, and chronic glomerulonephritis

Abbreviations: see TABLE 2

### TABLE 5  Distribution of MCP1 rs1024611 polymorphic variants in hemodialysis responders with or without diabetes

| Genotype | HD cases with diabetes (frequency), n = 175 | HD cases without diabetes (frequency), n = 426 | Odds ratio (95% CI) | 2-tailed $P$ | $P_{\text{trend}}$ | Power, % |
|----------|------------------------------------------|-----------------------------------------------|---------------------|-------------|------------------|---------|
| AA | 83 (0.47) | 201 (0.47) | | | | |
| AG | 76 (0.43) | 203 (0.48) | 0.907 (0.617–1.331) | 0.668 | | |
| GG | 16 (0.09) | 22 (0.05) | 1.761 (0.819–3.707) | 0.157 | | |
| AG+GG | 92 (0.53) | 225 (0.53) | 0.990 (0.685–1.431) | 1.000 | | |
| MAF | 108 (0.31) | 247 (0.29) | 1.093 (0.825–1.444) | 0.564 | | |

*adjusted for sex, age, and duration of renal replacement therapy

Abbreviations: see TABLE 2
TABLE 6 Distribution of MCP1 rs1024611 polymorphic variants in hemodialysed nonresponders with or without diabetes

| Genotype | HD cases with diabetes (frequency), n = 47 | HD cases without diabetes (frequency), n = 106 | Odds ratio (95% CI) | 2-tailed P* | P_respond | P_genotyping | Power, % |
|----------|------------------------------------------|-----------------------------------------------|---------------------|-------------|------------|--------------|----------|
| AA       | 21 (0.45) | 44 (0.42) | referent | -- | 0.862 | 0.880 |
| AG       | 21 (0.45) | 52 (0.49) | 0.874 (0.414–1.844) | 0.722 | -- | -- | 6.3 |
| GG       | 5 (0.11)  | 10 (0.09) | 1.203 (0.631–2.294) | 0.568 | -- | -- | 3.6 |
| AG+GG    | 26 (0.55) | 62 (0.58) | 0.902 (0.442–1.838) | 0.775 | -- | -- | 5.1 |
| MAF      | 31 (0.33) | 72 (0.34) | 0.957 (0.550–1.647) | 0.975 | -- | -- | 4.6 |

* adjusted for sex, age, and duration of renal replacement therapy

Abbreviations: see TABLE 2

the nondiabetic group. However, the observed difference in responsiveness was not related to the MCP1 −2518 G>A polymorphism.

We conclude that MCP1 −2518 A/G (rs1024611) polymorphism is not associated with responsiveness to hepatitis B vaccination in HD patients, independently of whether they have diabetic nephropathy or primary renal disease as a cause of ESRD. Therefore, determination of the MCP1 −2518 G>A polymorphism to explain non-responsiveness to hepatitis B vaccination in HD patients seems not to be useful in clinical practice. Lack of significance of the MCP1 −2518 G>A polymorphism in response to hepatitis B vaccination does not preclude its association with the development of anti-HBs in response to HBV infection. The involvement of the MCP1 −2518 G>A polymorphism in the outcome of HBV infection still remains controversial,13,16 and the issue requires further studies.

Supplementary material online Supplementary material is available at the journal’s website at www.pamw.pl.

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**SUPPLEMENTARY DATA**

**TABLE S1** Distribution of MCP1 rs1024611 genotypes in hemodialysis patients depending on the Hardy–Weinberg equilibrium

| MCP1 rs1024611 genotype frequencies | All HD cases | HD cases without diabetes | HD cases with diabetes |
|-------------------------------------|--------------|--------------------------|-----------------------|
|                                     | observed     | expected                 | observed              | expected     | observed | expected |
| responders to hepatitis B vaccine (n = 601) |             |                          |                       |             |         |         |
| AA                                  | 284 (0.47)   | 298 (0.50)               | 201 (0.47)            | 215 (0.50)  | 83 (0.47)| 84 (0.48)|
| AG                                  | 279 (0.46)   | 250 (0.41)               | 203 (0.48)            | 175 (0.41)  | 76 (0.43)| 75 (0.43)|
| GG                                  | 38 (0.07)    | 52 (0.09)                | 22 (0.05)             | 36 (0.09)   | 16 (0.09)| 17 (0.09)|
| P value*                            | 0.005        | 0.001                    | 0.814                 |             |         |         |
| nonresponders to hepatitis B vaccine (n = 153) |           |                          |                       |             |         |         |
| AA                                  | 65 (0.42)    | 67 (0.44)                | 44 (0.42)             | 46 (0.44)   | 21 (0.45)| 21 (0.45)|
| AG                                  | 73 (0.48)    | 68 (0.45)                | 52 (0.49)             | 48 (0.45)   | 21 (0.45)| 21 (0.44)|
| GG                                  | 15 (0.10)    | 17 (0.11)                | 10 (0.09)             | 12 (0.11)   | 5 (0.11) | 5 (0.11) |
| P value*                            | 0.398        | 0.335                    | 0.941                 |             |         |         |

*a for deviation from the Hardy–Weinberg equilibrium

Abbreviations: HD – hemodialysis

**TABLE S2** Distribution of MCP1 rs1024611 polymorphic variants in hemodialysis patients, diabetic hemodialysis patients, and nondiabetic hemodialysis patients compared with respective genotype frequencies in controls

| Genotype | HD patients (frequency) | Controls (frequency) | Odds ratio (95% CI) | 2-tailed P | P\text{\_}trend | P\text{\_}genotyping | Power, % |
|----------|-------------------------|----------------------|---------------------|------------|-----------------|----------------------|----------|
| all HD cases vs. controls | n = 754 | n = 437 |
| AA | 349 (0.46) | 225 (0.51) | referent | – | 0.260 | 0.117 | – |
| AG | 352 (0.47) | 177 (0.41) | 1.282 (0.995–1.653) | 0.055 | – | – | 52.9 |
| GG | 53 (0.07) | 35 (0.08) | 0.976 (0.603–1.595) | 1.000 | – | – | 4.8 |
| AG+GG | 405 (0.54) | 212 (0.49) | 1.232 (0.96561.570) | 0.096 | – | – | 40.0 |
| MAF | 458 (0.30) | 247 (0.28) | 1.107 (0.918–1.337) | 0.298 | – | – | 18.4 |
| HD cases without diabetes vs. controls | n = 532 | n = 437 |
| AA | 245 (0.46) | 225 (0.51) | referent | – | 0.388 | 0.055 | – |
| AG | 255 (0.48) | 177 (0.41) | 1.323 (1.008–1.738) | 0.043 | – | – | 56.3 |
| GG | 32 (0.06) | 35 (0.08) | 0.840 (0.486–1.448) | 0.590 | – | – | 13.8 |
| AG+GG | 287 (0.54) | 212 (0.49) | 1.243 (0.957–1.615) | 0.105 | – | – | 37.5 |
| MAF | 319 (0.30) | 247 (0.28) | 1.087 (0.888–1.331) | 0.436 | – | – | 12.6 |
| HD cases with diabetes vs. controls | n = 222 | n = 437 |
| AA | 104 (0.47) | 225 (0.51) | referent | – | 0.250 | 0.507 | – |
| AG | 97 (0.44) | 177 (0.41) | 1.186 (0.832–1.689) | 0.370 | – | – | 16.8 |
| GG | 21 (0.09) | 35 (0.08) | 1.298 (0.682–2.421) | 0.470 | – | – | 19.7 |
| AG+GG | 118 (0.53) | 212 (0.49) | 1.204 (0.860–1.687) | 0.297 | – | – | 19.8 |
| MAF | 139 (0.31) | 247 (0.28) | 1.157 (0.894–1.494) | 0.278 | – | – | 20.9 |

Abbreviations: CI – confidence interval, MAF – minor allele frequency, others – see TABLE S1
### TABLE S3  Distribution of MCP1 rs1024611 polymorphic variants in hemodialysis patients with or without diabetes

| Genotype | HD cases with diabetes (frequency), n = 222 | HD cases without diabetes (frequency), n = 532 | Odds ratio (95% CI) | 2-tailed P | P<sub>trend</sub> | Power, % |
|----------|------------------------------------------|---------------------------------------------|---------------------|------------|--------------|----------|
| AA       | 104 (0.47)                               | 245 (0.46)                                 | referent            | –          | 0.290        | 0.195    |
| AG       | 97 (0.44)                                | 255 (0.48)                                 | 0.896 (0.637–1.260) | 0.567      | –            | –        |
| GG       | 21 (0.09)                                | 32 (0.06)                                  | 1.546 (0.806–2.911) | 0.203      | –            | –        |
| AG + GG  | 118 (0.53)                               | 287 (0.54)                                 | 0.968 (0.699–1.343) | 0.904      | –            | –        |
| MAF      | 139 (0.31)                               | 319 (0.30)                                 | 1.064 (0.830–1.361) | 0.652      | –            | –        |

### TABLE S4  Demographic and clinical data in hemodialysis patients (n = 754) divided according to the genotypes of MCP1 rs1024611

| Parameter                                  | AA, n = 349 | AG, n = 352 | GG, n = 53 | P value between all groups |
|--------------------------------------------|-------------|-------------|-----------|---------------------------|
| male sex, n (%)                            | 217 (62.2)  | 197 (56.0)  | 25 (47.2) | 0.059<sup>a</sup>         |
| age, y                                     | 64 (17.4–93.1) | 64.8 (17–91.7) | 61.7 (17.9–87) | 0.911<sup>b</sup>          |
| diabetic nephropathy, n (%)                | 104 (29.9)  | 97 (27.6)   | 21 (39.6) | 0.200<sup>a</sup>         |
| chronic glomerulonephritis, n (%)          | 49 (14.1)   | 45 (12.8)   | 8 (15.1)  | 0.839<sup>a</sup>         |
| hypertensive nephropathy, n (%)            | 67 (19.2)   | 69 (19.7)   | 11 (20.7) | 0.965<sup>a</sup>         |
| chronic tubulointerstitial nephritis, n (%)| 37 (10.6)   | 31 (8.8)    | 8 (15.1)  | 0.330<sup>a</sup>         |
| polycystic kidney disease, n (%)           | 23 (6.6)    | 22 (6.2)    | 3 (5.7)   | 0.960<sup>a</sup>         |
| RRT vintage, y                             | 2.1 (0.05–19.1) | 2.3 (0.003–26.1) | 1.8 (0.04–22.7) | 0.776<sup>a</sup>         |

<sup>a</sup> χ<sup>2</sup> test  
<sup>b</sup> Kruskal–Wallis test

**Abbreviations:** RRT – renal replacement therapy

### TABLE S5  Distribution of MCP1 rs1024611 polymorphic variants in hemodialysis nonresponders without or with severe immunocompromise diseases compared with controls

| Genotype | Nonresponders (frequency) | Controls (frequency) | Odds ratio (95% CI) | 2-tailed P | P<sub>trend</sub> | Power, % |
|----------|---------------------------|----------------------|---------------------|------------|--------------|----------|
| **HD nonresponders without severe immunocompromise diseases vs. controls** | | | | | | |
| n = 133  | n = 437                   |                      |                     |            |              |          |
| AA       | 59 (0.44)                 | 225 (0.51)           | referent            | –          | 0.130        | 0.315    |
| AG       | 60 (0.45)                 | 177 (0.41)           | 1.293 (0.840–1.989) | 0.261      | –            | –        |
| GG       | 14 (0.11)                 | 35 (0.08)            | 1.525 (0.709–3.134) | 0.303      | –            | –        |
| AG + GG  | 74 (0.56)                 | 212 (0.49)           | 1.331 (0.885–2.007) | 0.180      | –            | –        |
| MAF      | 88 (0.33)                 | 247 (0.28)           | 1.255 (0.922–1.700) | 0.153      | –            | –        |
| **HD nonresponders with severe immunocompromise diseases vs. controls** | | | | | | |
| n = 20   | n = 437                   |                      |                     |            |              |          |
| AA       | 6 (0.30)                  | 225 (0.51)           | referent            | –          | 0.203        | 0.094    |
| AG       | 13 (0.65)                 | 177 (0.41)           | 2.754 (0.951–8.999) | 0.064      | –            | –        |
| GG       | 1 (0.05)                  | 35 (0.08)            | 1.071 (0.023–9.246) | 1.000      | –            | –        |
| AG + GG  | 14 (0.70)                 | 212 (0.49)           | 2.476 (0.873–7.997) | 0.097      | –            | –        |
| MAF      | 15 (0.38)                 | 247 (0.28)           | 1.523 (0.733–3.061) | 0.279      | –            | –        |

**Abbreviations:** see TABLES 1 and 2

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<sup>a</sup> adjusted for sex, age, and duration of renal replacement therapy

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POLSKIE ARCHIWUM MEDYCyny WEWNĘTRZNEJ
### TABLE S6
Comparison of MCP1 –2518 A>G polymorphism between the healthy population of different countries and ethnicity and our controls

| Studies in controls | Country               | Ethnicity          | **MCP1 –2518 A>G rs1024611** | **P**_trend |
|---------------------|-----------------------|--------------------|------------------------------|-------------|
|                     |                       |                    | **AA** | **AG** | **GG** | |
| Mostowska et al.¹   | Poland (Wielkopolska) | Caucasian          | 225   | 177   | 35     | referent |
| Ben-Selma et al.²   | Tunisia               | African            | 93    | 49    | 8      | 0.029    |
| Buraczyńska et al.³ | Poland (Lubelskie)    | Caucasian          | 209   | 101   | 15     | 0.0004   |
| Flex et al.⁴        | Italy                 | Caucasian          | 124   | 87    | 12     | 0.211    |
| Flores-Villanueva et al.⁵ | Korea       | Asian              | 66    | 74    | 22     | 0.007    |
| Karadeniz et al.⁶   | Turkey                | Caucasian          | 49    | 44    | 12     | 0.274    |
| Möller et al.⁷      | South Africa          | South African colored | 270   | 173   | 38     | 0.277    |
| Simeoni et al.⁸     | Germany               | Caucasian          | 1335  | 1043  | 190    | 0.742    |
| Szalai et al.⁹      | Hungary               | Caucasian          | 186   | 115   | 19     | 0.060    |
| Xu et al.¹⁰         | China                 | Asian              | 41    | 45    | 14     | 0.026    |
| Yang et al.¹¹       | United Kingdom        | Caucasian          | 36    | 60    | 8      | 0.019    |

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ARTYKUŁ ORYGINALNY

Polimorfizm białka chemotaktycznego dla monocytów typu 1 (MCP1 –2518 A/G) a odpowiedź na szczepienie przeciwko wirusowemu zapaleniu wątroby typu B u chorych hemodializowanych

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WPROWADZENIE Biały chemotaktyczny dla monocytów 1 (MCP-1) uczestniczy w patogenezie chorób nerek, cukrzycy, a także zakażenia wirusem zapalenia wątroby typu B (hepatitis B virus – HBV).

CELE Celem badania była ocena dystrybucji wariantów polimorficznych MCP1 –2518 A/G (rs1024611) u chorych poddawanych hemodializie (HD) w odniesieniu do stwierdzonej u nich odpowiedzi na szczepienie przeciwko wirusowemu zapaleniu wątroby typu B.

PACJENCI I METODY Chorzy leczeni HD, nigdy niezakażeni HBV, zostali zakwalifikowani do badania po przeprowadzeniu odpowiedniego szczepienia przeciwko wirusowemu zapaleniu wątroby typu B. Grupa leczonych HD składała się z 601 osób, które odpowiedziały na szczepienie wytworzeniem miana anty-HBs >10 IU/l uważanego za ochronne, i 153 osób, u których nie wystąpiła adekwatna odpowiedź poszczepiona (anti-HBs ≤ 10 IU/l). Wśród chorych, którzy odpowiedzieli na szczepienie, było 175 chorych na cukrzycę, a wśród chorych z brakiem adekwatnej odpowiedzi poszczepionej – 47 chorych na cukrzycę. Osoby zdrowe stanowiły grupę kontrolną (n = 437). Genotypowanie MCP1 wykonano przy użyciu łańcuchowej reakcji polimerazy–polimorfizmu długości fragmentów restrykcyjnych.

WYNIKI Częstości występowania wariantów polimorficznych MCP1 rs1024611 w grupie kontrolnej były następujące: 51% AA, 41% AG, 8% GG. Nie wykazano istotnych różnic (p >0,05) w dystrybucji genotypów MCP1 między żadną z badanych grup leczonych HD a kontrolną, niezależnie od występowania cukrzycy i odpowiedzi na szczepienie. Grupy leczone HD wyodrębnione na podstawie występowania cukrzycy lub rodzaju odpowiedzi na szczepienie nie różniły się pod względem dystrybucji genotypów MCP1.

WNIOSKI U chorych leczonych HD polimorfizm MCP1 –2518 A/G nie jest powiązany z odpowiedzią na szczepienie przeciwko zakażeniu HBV, niezależnie od występowania cukrzycy lub nie.

STRESZCZENIE

SŁOWA KLUCZOWE

białko chemotaktyczne dla monocytów 1, cukrzyca, hemodializa, MCP1 –2518 A/G rs1024611, szczepienie przeciwko wirusowemu zapaleniu wątroby typu B