ANALYSIS OF SINGLE-NUCLEOTIDE POLYMORPHISMS OF SERUM PROTEINS IN INFLAMMATION: THE ASSOCIATION OF FETUIN-A rs4917 and rs4918 POLYMORPHISMS WITH CARDIOVASCULAR DISEASE AND MANNOSE BINDING LECTIN 2 (MBL2) GENE POLYMORPHISMS AND ITS ASSOCIATION WITH CLINICAL MANIFESTATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Ph.D Thesis

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Introduction

Fetuin-A, also called AHSG (Alpha 2-HS Glycoprotein) is a multifunctional serum glycoprotein which belongs to the cystatin superfamily. Contrary to few reports, many authors suggest that Fetuin-A is associated with cardiovascular diseases and it has been implicated in several diverse functions including the process of atherosclerosis. Associations of its polymorphisms with myocardial infarction and risk factors are temporarily little-known.

Systemic lupus erythematosus (SLE) is a multi-factorial chronic autoimmune disorder. The exact etiology of SLE is still unknown. Multiple genes confer susceptibility to disease development. A role for mannose binding lectin (MBL) in autoimmune diseases has been demonstrated earlier and elevated level of MBL has been shown in systemic lupus erythematosus (SLE) patients. The role of MBL in the pathogenesis of SLE has so far not been clearly defined. MBL deficiency is linked to susceptibility to secondary infections and can be a contributory factor in the development of different autoimmune diseases.

Aim

In these cross-sectional studies of patients with previous ST-segment myocardial infarction (pMI group), we aimed to investigate the distribution of rs4917 and rs4918 SNPs of AHSG gene and their associations with clinical features. The allele distributions were compared between pMI patients, healthy controls and a reference group.

In our study, we intended to determine the association of rs4917 and rs4918 SNPs with parameters of obesity (body mass index [BMI]), lipid status (total, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides), proinflammatory cytokines (tumor necrosis factorα [TNFα]), and adipokines (adiponectin, resistin), in patients with previous ST-segment myocardial infarction and healthy controls .

In our work, we aimed to describe the allele distribution of *MBL2* haplotypes: SNPs in the first exon of the gene, B, C and D, collectively labeled O, whereas the major alleles at these loci have been called A and a SNP in the promoter region X, Y (located 221 bp before the transcription start site) in 315 SLE patients from Hungary and 182 geographically matched healthy controls. Clinical (cutan lupus, arthritis, lupus nephritis, serositis (pleuritis, pericarditis), neuropsychiatric and hematologic disorders) and laboratory characteristics were registered and correlated to the MBL2 genotypes. Since some data indicate that juvenile-onset SLE may have specific clinical, immunological and genetic traits, the analysis was extended to the possible differences between juvenile-onset (≤ 20 years at the time of diagnosis) and adult-onset SLE.

Methods

Eighty two healthy controls (inclusion criteria were as follows: healthy status (by physical examination), leanness (BMI <30 kg/m2), and normal values during laboratory testing, aged 60.1±6.9 years) and 157

patients with previous ST-segment myocardial infarction (6 to 24 months prior to the start of the study, aged 59.4±12.2 years) were enrolled in the AHSG study. Two hundred and thirty nine unrelated individuals, all other, non CVD illness diagnosed (aged 41.8 ± 22.2 years) were entered in the analysis of rs4917 and rs4918 allele distribution and considered as reference group.

The pMI group subdivided into 42 obese and 115 normal-weight subjects. Subjects are considered obese had BMI greater than or equal to 30 kg/m^2. Forty nine patients were diagnosed with diabetes mellitus. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR, HOMA-A) was calculated according to the formula: $IR_{HOMA} = (I_0 \times G_0)/ 22.5$, where I_0 is fasting insulin (IU), G_0 is fasting glucose (mmol/l) (as described by Mathews). Pancreatic β-cell function (HOMA-B) was determined as follows: $HOMA\text{-}B = 20 \times I_0/ G_0 - 3.5$.

The single-nucleotide polymorphisms rs4917 and rs4918 genotyping was carried out using the Competitive Allele Specific polymerase chain reaction genotyping system assay (KASP). Serum AHSG concentration was determined by radial immunodiffusion. Fasting serum samples were used to examine standard clinical laboratory measurements. Serum TNFα, resistin and leptin were measured by enzyme-linked immunosorbent assay. Adiponectin and C-peptide levels were measured with radioimmunoassay. Insulin concentration was measured by insulin direct human enzyme-linked immunosorbent assay kit.

The MBL2 study was performed in 315 patients with SLE. The patients were cared in three different centers. Sixty-five patients attended the 3rd Department of Internal Medicine (center A), 55 patients attended the Central Laboratory of Immunology, Semmelweis University (Actually: Department of Laboratory Medicine, center B) while 195 patients attended the outpatient department of the Clinic of Immunology and Rheumatology, University of Pécs (center C). Age at the diagnosis was set to this date (26 male, 279 female; age at the study: median 44 years, interquartile range 35.3-53.8 years). All patients fulfilled ≥4 classification criteria of the American College of Rheumatology (ACR) of SLE. Disease activity was determined by using the SLE Disease Activity Index (SLEDAI). 182 healthy volunteers (75 males, 107 females, 48.5 (41.0–56.0 years old)) were included in the study as controls. The MBL2 alleles were genotyped by means of polymerase chain reaction with the use of sequence-specific priming exactly as described by Garred et al. In exon 1 of the MBL2 gene, the presence of three single-base substitutions was investigated at codon 54 (the B allele), codon 57 (the C allele), and codon 52 (the D allele). The structural variant alleles are given the common designation O while the normal allele is given an alias A. A down-regulating promoter polymorphism at position −221 (Y to X) of the MBL2 gene was also included. This variant is exclusively present in front of a normal A allele and is not present in front of variant alleles. Thus, we also used

the term Y/Y, Y/X, and X/X when appropriate which in fact indicate X against all other haplotypes.

Results

Allelic distribution of pMI group, healthy controls and reference group was determined. They did not differ significantly from each other. We found no statistically significant differences in the C/T or C/G nucleotide frequencies studied when categorized by groups.

During multiple comparisons, we observed significant differences in LDL cholesterol and TNFα levels in the healthy control group. There was a trend of serum total cholesterol decreasing with the presence of the T allele. On pairwise analysis, members with CC had higher LDL cholesterol and TNFα levels than TT homozygotes (Mann- Whitney U test, $p = 0.017$ in both parameters). The presence of the T nucleotide was also associated with lower total cholesterol (4.08 ± 0.51 vs 5.41 ± 0.86 mmol/L, $p = 0.018$), LDL cholesterol (2.28 ± 0.32 vs. 3.39 ± 0.44 mmol/l, $p = 0.020$), and TNFα levels than non-T nucleotide (3.90 ± 0.021 vs 4.10 ± 0.24 pg/mL, $p = 0.010$).

G-nucleotide carriers had significantly lower serum TNFα (4.10 ± 0.23 vs. 3.85 ± 0.22 pg/ml, $p = 0.003$), adiponectin (12.4 ± 3.14 vs. 14.3 ± 2.30 μg/ml, $p = 0.047$), and higher leptin (13.9 ± 9.23 vs. 10.7 ± 9.19 ng/ml, $p = 0.036$) concentrations than in non-G carriers. Other parameters, including Fetuin-A concentrations, did not differ significantly.

Elevated serum Fetuin-A (673 ± 111 mg/l vs. 619 ± 97 mg/l, p < 0,001), TNFα, ghrelin, leptin, C-peptide, C-peptide/glucose, glucose and insulin was observed among the pMI group. We did not observe any significant associations between laboratory parameters and rs4917 or rs4918 polymorphisms.

BMI and abdominal circumference showed a trend toward lower values with the T allele. Indeed, T carriers (n = 76) had significantly lower BMI (27.2 ± 4.6 vs 28.6 ± 3.8 kg/m2, p = 0.019) and abdominal (101 ± 12 vs 103 ± 10 cm, p = 0.040) and waist circumferences (102 ± 9 vs 106 ± 8 cm, p = 0.003) than did those who had no T nucleotide (n = 81) in rs4917. The T nucleotide was more frequent in non-obese than in obese patients (χ^2 = 5.217, p = 0.022). It is interesting, however, that TNFα concentration can differ significantly even in sera of healthy persons with normal BMI, that is, the C allele is associated with higher TNFα levels than the T allele. This difference could not be detected in pMI group probably because of the existing subclinical inflammation and prevalence of obesity among patients.

There was a trend towards lower values of obesity in patients with the G allele. Indeed, G-carriers had significantly lower BMI (27.3 ± 4.6 vs. 28.6 ± 3.8 kg/m^2, p=0.017) and waist circumference (102 ± 9 vs. 106 ± 8 cm, p=0.002) than those without the G nucleotide. Other parameters, including abdominal circumference (101 ± 12 vs. 104 ± 10 cm, p=0.168), did not differ significantly. The minor allele G was found to be more frequent in lean (62/114) than in obese patients (14/43, (χ^2:

5.957, RR=1.067, 95% CI=1.053–2.651, p=0.015). Association between BMI and rs4918 polymorphism (CC, CG, and GG genotypes, and G allele) could be observed among patients without diabetes but not in diabetics. In addition, a strong linearity between the frequency of the G allele and lower BMI could be identified. Subgroup analysis of the anthropometric and metabolic parameters in obese patients according to different genotypes and alleles did not result in significant statistical differences.

There were 49 patients with T2DM in pMI group. They differed from the nondiabetic patients (n = 108) only in parameters of insulin resistance, that is, glucose (7.19 ± 2.13 vs. 5.03 ± 0.68 mmol/l, $p < 0.001$), insulin (28.3 ± 16.3 vs. 21.7 ± 14.08 μU/ml, p = 0.008), C-peptide (3.91 ± 2.25 ng/ml vs. 3.00 ± 2.13 ng/ml, p = 0.008), HOMA-IR (7.69 ± 3.46 vs. 4.67 ± 3.04, $p < 0.001$), and HOMA-B (191 ± 133 vs. 260 ± 147, p = 0.004) but not in those of obesity: BMI and abdominal circumference or waist circumference. The small sample size did not allow comparison either of CC and TT or GG homozygotes or C- and non-C carriers within the diabetic group.

The percentage distribution of carriers of the homozygous normal exon 1 MBL2 allele (A/A), variant allele heterozygous carriers (A/O), variant allele homozygotes (O/O) as well as the carrier's status of the Y/X promoter allele were determined in 315 SLE patients and 182 healthy controls, respectively. There was no significant difference between the

two groups either in the distribution of the A/A, A/O, and O/O carriers, the proportion of the carriers of the B variant allele, or alleles of X/Y promoter polymorphism. All alleles tested in both patients and controls were in Hardy–Weinberg equilibrium. We analyzed the age distribution at diagnosis of the 315 SLE patients tested according to the MBL2 genotype. No significant difference in this variable was found among carriers of structural variants genotype and allele frequencies.

There was a significant (p=0.017, Kruskal–Wallis test) difference among X/X homozygotes, Y/X heterozygotes, and Y/Y homozygotes in the age at the onset of SLE. The median (interquartile range) of age at disease onset was 23.0 (17.0–38.0) years, 33.5 (23.0–43.8) years, and 28.0 (21.5– 39.5) years, respectively, indicating that there is a marked difference in the age at diagnosis between XX homozygotes (n=23) and the rest of the patients. In order to test this assumption, the age limit between juvenile-onset and adult-onset SLE was set first at 20 years of age, patients who were 20 years old or younger at the time of diagnosis were considered to have juvenile-onset SLE while the rest of the patients were considered to have adult-onset disease. We observed a highly significant (p=0.004) difference between homozygous X allele carriers on the one hand and carriers of the Y allele. X/X genotype carriers occurred more frequently in the juvenile-onset group than in the adult-onset group. In addition, X/X homozygotes occurred more frequently (p=0.0003) in juvenile-onset SLE patients (17.4%) than in the group of healthy controls (6.0%) whereas no significance difference

between adult-onset SLE patients (5.6%) and controls was found (p= 0.840).

In contrast, we did not find a difference between the two groups in the frequency of the normal and structural variant allele carriers in general.

Considering the differences between the two clinical subgroups in the frequency of the X/X genotype, we performed multiple regression analysis with the gender of the patients as well as differences among the participating centers found to be of marginal significance at univariate analysis as independent parameters. The X/X genotype was found to be independently associated with the age at diagnosis even after these adjustments. The odds ratio for having juvenile-onset SLE of the X/X carriers was more than 3 as compared to the rest of patients. The same differences were found when we set the limit of the adult-onset and juvenile-onset SLE at younger age. When ≤18 years old (juvenile) and > 18 years old (adult) patients were compared, X/X homozygotes were found in 8/23 (34.8%) and 24/292 (8.2%) of the patients, respectively (p < 0.001).

In addition to the genetic associations, however, we did observe some clinical characteristic differences between juvenile-onset (< 20 years) and adult-onset (≥20 years) patients. Joint involvement occurred significantly more frequently (p=0.018) among patients of the former group and a similar tendency was recorded in the development of renal manifestation as well.

Development of six types of clinical manifestations (cutaneous, arthritis, renal, serositis (pleuritis/pericarditis), neuropsychiatric, and hematological) between establishment of diagnosis and the time of study was registered. Distribution of these manifestations according to MBL2 genotypes was examined. No difference among the normal and structural variant genotypes was observed in the development of either organ manifestation.

By contrast, the findings indicated that development of organ manifestations is influenced by the X/Y promoter polymorphism. Cutaneous manifestations and serositis developed more frequently in the X/X homozygotes ($p=0.003$; $p=0.013$) compared to X/Y and Y/Y carriers and in only a lesser extent in Y/X heterozygotes than the Y/Y homozygotes, and a similar albeit not significant tendency was observed in the case of renal manifestations. The X MBL2 promoter polymorphism remained significantly associated with the risk of development of cutaneous manifestations even after adjustment to age at the time of study, gender, SLEDAI score, and differences between the participating centers. Neither the occurrence of antiphospholipid- nor anti-DNA antibodies was related to the different MBL2 genotypes.

Our conclusions

This study provides data on rs4917 and rs4918 nucleotide frequencies in Hungary. The frequencies of the C/T variants of rs4917 and C/G of rs4918 are in the range of the reported frequencies in Europe: 0.65/0.35 (range: 0.596/0.404, Great Britain and 0.786/0.214, Iberia), for both

alleles. The association of the T nucleotide with more favorable anthropologic parameters (BMI and abdominal and waist circumferences) could be observed in pMI, essentially in the subgroup without diabetes. Leanness, again, was associated with higher prevalence of the T allele. In healthy controls, T-nucleotide carriers had lower low-density lipoprotein cholesterol levels compared with non-T carriers and the serum concentration of TNFα was found to be higher carrying the non-T allele.

Our results suggest that in rs4918 SNP of Fetuin-A, the presence of the G nucleotide is associated with lower serum TNFα and adiponectin and higher leptin concentrations in healthy subjects compared to that of the C nucleotide. In the pMI group, waist circumference and BMI values were lower in G-carriers than in C-carriers. In the pMI group, the association between the rs4918 polymorphism and obesity was relevant only in patients without diabetes. In summary, our results are in accord with the observations that the minor variant T of rs4917 and the minor variant G of rs4918 respectively is linked with more favorable parameters than the C allele. Our observations are in accord with those that find AHSG correlate much more with obesity than with diabetes mellitus. Large-scale prospective studies could determine the causative relationship and functional impact of AHSG variants in different populations.

We did not find significant differences between SLE patients and healthy controls in the distribution of the MBL2 structural exon 1

polymorphisms. Within the group of patients, we found that homozygotes for an MBL2 down-regulating promoter polymorphism at position −221 (YA to XA) (rs7096206) were significantly (p=0.017) younger at diagnosis than the other patients. The frequency of juvenile-onset SLE (≤ 20 years) was particularly high among XA/XA homozygotes (17.4%) as compared to the rest of the patients (5.6%) (p=0.004). XA/XA carriers did have significantly higher risk of development of cutaneous manifestations (p=0.003) and pleuritis/pericarditis (p=0.013) as compared with the rest of the patients. These data indicate that MBL may act as a disease modifier in SLE patients through a mechanism to be identified.

Publications of György Temesszentandrási

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