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Association of Monocyte Chemoattractant Protein-1 (MCP-1) 2518 A/G Polymorphism with Obesity in Korean Type 2 Diabetes Mellitus

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Purpose: Monocyte chemoattractant protein-1 (MCP-1) is a member of the CC chemokine family, and the MCP-1 2518 A/G gene polymorphism is reported to be correlated with chronic inflammatory diseases, including insulin resistance and metabolic syndrome. However, few studies have investigated the association between MCP-1 gene polymorphisms and obesity in patients with type 2 diabetes mellitus (T2DM). We conducted a retrospective case-control study and evaluated the association between the MCP-1 2518 A/G polymorphism and obesity in Korean patients with T2DM.

Patients and Methods: This single-center, retrospective, case-control study enrolled 526 Korean patients with T2DM. Obesity was defined using the body mass index (BMI) with a cutoff level of 25 kg/m^2. Polymerase chain reaction-restriction fragment length polymorphism was used to analyze MCP-1 2518 A/G polymorphism; the genotypes was presented as GG, AG, or AA. We compared the MCP-1 2518 A/G polymorphism with the prevalence of diabetic complications, as well as clinical and biochemical characteristics.

Results: The obese group had a higher number of females and higher C-peptide, insulin, triglycerides, aspartate transaminase (AST), and alanine transaminase (ALT) levels. The obese group also had a higher prevalence of cardiovascular disease than the non-obese group. The obese group had a higher frequency of the MCP-1 2518 AA genotype and the A allele than the non-obese group. The results of multiple logistic regression analysis showed that the non-G allele of MCP-1 was significantly associated with obesity (odds ratio (OR), 1.888; P=0.016).

Conclusion: This study demonstrates that the MCP-1 2518 A/G polymorphism is associated with obesity in Korean patients with T2DM. Further studies involving various ethnic groups are required to validate our results.

Keywords: obesity, MCP-1 protein, polymorphism, diabetes mellitus

Introduction

Obesity is increasing at an alarming rate worldwide owing to changes in lifestyle and eating habits. According to the World Health Organization, approximately 30% of the world's population was considered overweight or obese in 2020.[1] The prevalence of obesity in Korea is comparable to the global prevalence, and increased from 31.4% in 2009 to 38.3% in 2020. In addition, the prevalence of obese individuals with a body mass index (BMI) of 35kg/m2 or higher tripled to 26.3% in 2021. The prevalence of obesity also differs by sex, with 48% in the male population and 27.7% in the female population.[2] The obesity rate among patients with type 2 diabetes mellitus (T2DM) is reported to be approximately 50%. The obesity rate of patients with T2DM in Korea is 54.4%: 12.9% for class II obesity, with a BMI of 30kg/m2 or higher, and 1.9% for class III obesity, with a BMI of 35 kg/m2 or higher.[3]

Obesity induces a chronic inflammatory response by increasing the production of adipokines and various inflammatory cytokines owing to the excessive accumulation of adipocytes in the body. Leptin, resistin, and adiponectin are

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adipokines that are secreted by adipocytes. Adiponectin is closely associated with obesity and is markedly reduced in obese patients. Adiponectin is responsible for anti-inflammatory reactions, such as reducing the expression of adhesion molecules, and plays a role in inhibiting atherosclerosis.[4] Therefore, atherosclerosis may occur more easily in obese patients with reduced adiponectin levels than in healthy individuals. Obesity in diabetes causes intravascular atherosclerosis due to reduced adiponectin and increased leptin production, which increases the incidence of chronic diabetic complications.[5] Therefore, active weight management is necessary for patients with diabetes.

Monocyte chemoattractant protein-1 (MCP-1) is a CC chemokine that was discovered in 1989 and plays a pivotal role in the development of inflammation.[6] Key factors in MCP-1 production are cytokines, such as tumor necrosis factor-alpha (TNF-α) and inter-leukin (IL)-1β, which are secreted from excessively accumulated adipocytes. In addition, an increase in oxidative stress, such as high blood glucose levels and ischemia, is known to result in an increase in MCP-1 production.[7] MCP-1 has been reported to be involved in major pathophysiological mechanisms of chronic inflammatory diseases, such as cerebral infarction, myocardial infarction, diabetes, and chronic arthritis.[8] The mechanism through which MCP-1 causes chronic inflammatory diseases involves continuous inflammatory induction and responses in the body. In patients with cerebral and myocardial infarctions, the serum MCP-1 concentration is increased, and there is an inverse correlation between the severity of the disease and the concentration of serum MCP-1, indicating that MCP-1 plays an important role in chronic inflammatory disease.[9,10]

Obesity is a state in which chronic inflammatory reactions occur in the body, and several studies have reported an association between MCP-1 and obesity. It has been reported that the expression of MCP-1 in visceral and subcutaneous fat tissues increase and the concentration of MCP-1 in the serum increases in obese patients.[11,12] Youngce et al suggested that adipocyte generation increases when MCP-1 is administered.[13] In addition, the direct administration of MCP-1 in animal models has been reported to increase insulin resistance and adipocyte activation.[14]

Meanwhile, an association between the serum concentration of MCP-1 and the MCP-1 2518 A/G polymorphism has been reported, suggesting an association between MCP-1 and chronic inflammatory diseases. In particular, studies have reported an association between insulin resistance and MCP-1 gene polymorphisms in diseases that are associated with major pathophysiological mechanisms. In Korea, a correlation between poly-cystic ovarian syndrome and MCP-1 2518 A/G polymorphism has been reported.[15] However, a study demonstrated that MCP-1 gene polymorphisms may differ according to race.[16] MCP-1 gene polymorphisms exhibit a correlation with insulin resistance in both non-diabetic and diabetic patients; however, the results indicating its association with weight differ among studies.[17] Several studies have suggested that MCP-1 gene poly-morphism is related to insulin resistance; however, very few studies related to obesity have investigated the related MCP-1 serum concentrations. Obesity can lead to or worsen diabetic complications; therefore, the evaluation of screening factors is essential.

In this study, we aimed to evaluate the relationship between MCP-1 2518 A/G poly-morphism and obesity in Korean patients with T2DM.

Materials and Methods

Study Design and Participants

This single-center, retrospective, case-control study enrolled 526 Korean patients with T2DM. Among the enrolled patients, 262 were female and 264 were male. The average duration of diabetes was approximately 12 years. Obesity was evaluated based on the BMI. The BMI was defined as the value obtained by dividing the patient's weight (kg) by the square of the patient's height (m^2). We placed patients with a BMI of 25 kg/m^2 or more in the obese group and those with a BMI of 25 kg/m2 in the non-obese group based on the Asia-Pacific guidelines. A total of 241 participants were classified as obese, and 285 were classified as non-obese. We compared the MCP-1 2518 A/G polymorphism with the prevalence of diabetic complications, as well as clinical and biochemical characteristics.

Genotyping of MCP-1 Gene Polymorphic Variants

DNA samples were collected from each participant and PCR was performed. Approximately 100 ng genomic DNA was mixed with 0.2 mmol/L primers (Forward primer: 5'-GCTCCGGGCCCAGTATCT-3' and reverse primer: 5'-

ACAGGGAAGGTGAAGGGTATGA-3'), 1.5 mmol/L MgCl2, 0.2 mmol/L dNTPs, and 1 U GoTaq Hot Start Polymerase (Promega Corporation, Madison, WI, USA). The process had 3 main steps: Denaturation; heating the solution to 95 °C. Annealing: The sample was cooled to 59 °C for 30s and 72 °C for 50s. Extension: This cycle was repeated approximately 36 times. The 236 bp PCR products that were fully digested into 182 and 54 bp fragments (homozygous cut) using the Fermentas restriction enzymes were interpreted as the GG genotype. The 236 bp PCR fragments that were incompletely digested due to a lack of recognition sequences were interpreted as the AA genotype (no cut).

Statistical Analyses

Statistical analyses were performed using SPSS for Windows (version 22.0; IBM Corp., Armonk, NY, USA). The Chi-square test was used to calculate the probability of Hardy-Weinberg equilibrium. To evaluate the differences between the two groups, the Stu-dent's *t*-test was used for continuous variables and the Chi-square test was used for categorical variables. Multiple logistic regression analysis was used to investigate the relationships between obesity and genotype, sex, age, diabetes duration, hypertension (HTN), dyslipidemia, and hemoglobin A1c (HbA1c). A P-value of <0.05 was considered statistically significant.

Ethics Statement

Written informed consent was obtained from all participants. This study was approved by the Institutional Review Board of the Chungbuk National University Hospital (IRB No. 2017–10-009-009). The current study was conducted according the guidelines administered by the Declaration of Helsinki.

Results

Baseline Characteristics of the Patients

The demographic and biochemical characteristics of the patients according to their BMI (non-obese vs obese) are presented in Table 1. The average BMI of the non-obese group was 22.6 ± 1.7 kg/m^2, whereas that of the obese group was 27.8 ± 2.8 kg/m^2. The proportion of female patients was higher in the obese group than in the non-obese group (56.4% vs 44.2%, P=0.005). The prevalence of HTN (68% vs 55.4%, P=0.003) was statistically higher in the obese group. According to the laboratory findings, the aspartate aminotransferase (AST) (28.6±15.2 vs 25.5±13.4, P=0.013), alanine aminotransferase (ALT) (33.9±24.1, 27.5±22.0, P=0.002), and triglyceride levels (171.9±107.2 vs 150.6±87.4, P=0.017) were higher in the obese group than those in the non-obese group. C-peptide and insulin concentrations were relatively high in the obese group, but no statistical difference was observed between the two groups in terms of the

Table 1 Baseline Characteristics of Enrolled Patients

	Non-Obese (n =285)			Obese (n=241)			*P*-value
Demographic Factors							
Age (years)	60.1	±	10.2	59.3	±	11.2	0.421
Female sex, N (%)	126 (44.2)			136 (56.4)			0.005
BMI (kg/m2)	22.6	±	1.7	27.8	±	2.8	0.000
Past Medical History							
Duration of DM (years)	12.7	±	8.2	11.4	±	7.0	0.064
HTN, N (%)	158 (55.4)			164 (68)			0.003
Dyslipidemia, N (%)	120 (42.1)			133 (55.2)			0.003

(*Continued*)

Table 1 (Continued).

	Non-Obese (n =285)			Obese (n=241)			*P*-value
Clinical Factors							
C-peptide (ng/mL)	2.4	±	1.9	2.9	±	2.2	0.025
Insulin (mIU/L)	11.6	±	7.7	13.9	±	12.3	0.040
HbA1c (%)	7.6	±	1.3	7.4	±	1.2	0.104
eAG (mg/dL)	163.7	±	28.0	160.1	±	27.3	0.153
FBS (mg/dL)	135.8	±	41.0	133.6	±	43.4	0.597
PP2 (mg/dl)	212.3	±	72.0	208.6	±	66.6	0.629
HOMA-IR	2.7	±	3.0	2.6	±	4.3	0.802
BUN (mg/dL)	16.1	±	8.7	15.2	±	6.8	0.195
Creatinine (mg/dL)	1.1	±	0.6	1.1	±	0.6	0.892
Total cholesterol (mg/dL)	173.6	±	32.8	169.9	±	35.3	0.214
Triglycerides (mg/dL)	150.6	±	87.4	171.9	±	107.2	0.017
HDL-cholesterol (mg/dL)	48.3	±	12.7	46.9	±	12.8	0.223
LDL-cholesterol (mg/dL)	102.4	±	28.7	100.6	±	29.1	0.500
AST (IU/L)	25.5	±	13.4	28.6	±	15.2	0.013
ALT (IU/L)	27.5	±	22.0	33.9	±	24.1	0.002
ALP (IU/L)	205.7	±	73.2	197.7	±	64.9	0.188
Bilirubin (mg/dL)	0.7	±	0.3	0.7	±	0.3	0.432

Notes: Data are expressed as the mean ± standard deviation (SD).
Abbreviations: N, number; BMI, body mass index; DM, diabetes mellitus; HTN, Hypertension; HbA1c, hemoglobin A1c; eAG, estimated average glucose; FBS, Fasting blood sugar; PP2, post-prandial 2-h glucose; HOMA-IR, homeostatic model assessment for insulin resistance; BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate amino-transferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

homeostatic model assistance for insulin resistance (HOMA-IR), which indicates insulin resistance. There were also no significant differences in the blood sugar, HbA1c, or cholesterol levels between the two groups.

Diabetic Complications According to BMI

Diabetic neuropathy, retinopathy, and nephropathy, which are diabetic microvascular complications, were not significantly different between the two groups (Table 2). Among the macrovascular complications of diabetes, cardiovascular disease was significantly more common in the obese group (17.8% vs 10.2%; P=0.011), while there was no significant difference in the prevalence of cerebrovascular disease.

Table 2 Prevalence of Diabetic Complications According to BMI

Complications, N (%)	Non-Obese (n =285)	Obese (n=241)	*P*-value
Macrovascular complications			
Cerebrovascular disease	26 (9.1)	18 (7.5)	0.495
Cardiovascular disease	29 (10.2)	43 (17.8)	0.011
Microvascular complications			
Diabetic neuropathy	127 (44.6)	91 (37.8)	0.115
Diabetic retinopathy	109 (38.2)	92 (38.2)	0.987
Diabetic neuropathy	86 (30.2)	82 (34.4)	0.297

Notes: Data are expressed as numbers (%). P-values were calculated using the Chi-square test.

Table 3 Association Between Genotypes of MCP-1 Polymorphism and Obesity

Variables, N (%)	Non-Obese (n =285)	Obese (n=241)	*P*-value
Genotype			0.022
AG+GG	254 (89.1)	198 (82.2)	
AA	31 (10.9)	43 (17.8)	
Allele			0.046
A	200 (35.1)	198 (41.1)	
G	370 (64.9)	284 (58.9)	

Notes: Data are expressed as numbers (%). p-values were calculated using the Chi-square test.
Abbreviation: MCP-1, monocyte chemoattractant protein-1.

Distribution of MCP-1 2518 A/G Polymorphism

The distribution of the MCP-1 2518 A/G polymorphism comprised the AA genotype (14.1%, n=74), AG genotype (47.5%, n=250), and GG genotype (38.4%, n=202) (Table 3). The obese group exhibited a relatively high rate of the AA genotype (17.8% vs 10.9%; P=0.022) compared to the non-obese group (Figure 1A). The MCP-1 2518 A/G polymorphism distribution followed the Hardy-Weinberg equilibrium principle. The frequency of MCP-1 gene alleles exhibited different patterns relative to BMI. The frequency of the A allele was higher in the obese group than that in the non-obese group (P =0.046) (Figure 1B).

Multiple Logistic Regression Analysis: Risk Factors of Obesity

Multiple logistic regression analysis was performed to determine the effects of various risk factors, including genotypes, on obesity (Table 4). The non-G allele of MCP-1 was significantly associated with obesity (odds ratio (OR), 1.888; P=0.016). Among the other parameters, significant associations with obesity were observed in females, patients with HTN, and patients with dyslipidemia ((OR): 1.728, 1.943, and 1.529, respectively; P=0.003, P=0.001, and P=0.022, respectively).

Discussion

In this study, the MCP-1 AA genotype was frequently observed in obese patients, confirming that the MCP-1 2518 A/G polymorphism is related to obesity in Korean patients with T2DM. To date, no studies have reported the association between obesity and the MCP-1 2518 A/G polymorphism in patients with T2DM.

One of the key findings of this study is the association between the MCP-1 AA genotype and obesity. The frequency of the AA genotype was significantly higher in the obese group compared to the non-obese group, consistent with previous studies that demonstrated a relationship between MCP-1 polymorphisms and obesity-related metabolic conditions. The role of MCP-1 in mediating inflammatory processes and adipocyte accumulation may explain this association.

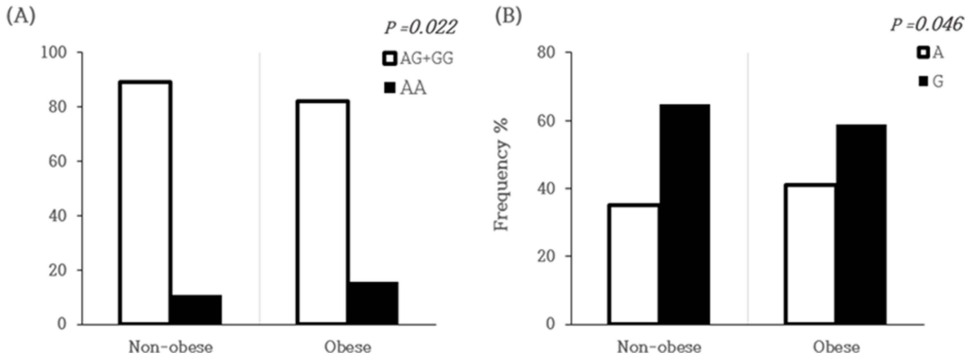

Figure 1 Frequency of monocyte chemoattractant protein-1 (MCP-1) polymorphism according to the presence of obesity (**A**) Distribution of genotypes of MCP-1 gene (**B**) Frequency of alleles of MCP-1 gene. The P-values were calculated using the Chi-square test.

Table 4 Risk Factors of Obesity

Variables	OR (95% CI)	*P*-value
Non-G allele	1.888 (1.126–3.165)	0.016
Female sex	1.728 (1.202–2.485)	0.003
Age[a]	0.894 (0.754–1.060)	0.199
Duration of DM[b]	0.810 (0.637–1.032)	0.088
HTN	1.943 (1.311–2.880)	0.001
Dyslipidemia	1.529 (1.064–2.980)	0.022
HbA1c[c]	0.870 (0.751–1.007)	0.062

Notes: [a]Risk associated with a 10-y increase in age; [b]Risk associated with a 10-y increase in the duration of DM; [c]Risk associated with a 1(%) increase in HbA1c.
Abbreviations: OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; HbA1c, hemoglobin A1c.

MCP-1 has been shown to influence the development of insulin resistance and promote adipose tissue inflammation, both of which are central to the pathophysiology of obesity.

Insulin resistance associated with the MCP-1 2518 A/G polymorphism has been demonstrated in obese Japanese patients with T2DM and in a cohort study of German patients with T2DM.[17,18] However, in these studies, the C-peptide and insulin levels were significantly higher in the obese group, while HOMA-IR levels were not statistically significant; therefore, the association between the MCP-1 2518 A/G polymorphism and insulin resistance could not be revealed. These studies were not sufficient to demonstrate the association between the number of recruited patient groups, and HOMA-IR levels may have been affected by differences in age and sex. In addition, considering that genotyping may vary between races, a large cohort study on the association between the MCP-1 2518 A/G polymorphism and insulin resistance is necessary in various ethnic groups.

MCP-1, also known as CCL2, is a key CC chemokine involved in recruiting monocytes and other immune cells to sites of inflammation by binding to the CCR2 receptor.[6] It is produced by various cells, including adipocytes, in response to inflammatory stimuli like TNF-α and IL-1β. In obesity, excessive adipocyte accumulation leads to increased MCP-1 production, contributing to chronic inflammation and metabolic complications such as T2DM and cardiovascular disease. Elevated MCP-1 levels are linked to insulin resistance, atherosclerosis, and diabetic complications.[9,10] Polymorphisms in the MCP-1 gene, such as the 2518 A/G variant, are associated with differences in MCP-1 expression and susceptibility to inflammatory conditions.

Obesity is a low-grade chronic inflammatory state characterized by activated macro-phages. MCP-1 released from adipocytes is known to be a key mediator in this inflammatory process. Serum MCP-1 is highly expressed in chronic inflammatory diseases, such as cerebral infarction, myocardial infarction, diabetes, chronic arthritis, and obesity.[8] Previously, Kouyama and Simeoni et al confirmed that the MCP-1 2518 A/G poly-morphism is related to a low serum MCP-1 concentration, but this study did not directly measure the serum MCP-1 concentration; therefore, it was not possible to confirm the relationship between the MCP-1 2518 A/G polymorphism and serum MCP-1 concentrations in T2DM.[17,18] Therefore, measurement of the concentration of MCP-1 should be further considered to describe the role of serum MCP-1 in MCP-1 2518 A/G polymorphism and obesity.

A comparison of the prevalence of diabetic complications according to obesity in patients with T2DM demonstrated that diabetic neuropathy, retinopathy, nephropathy, and cerebrovascular disease did not differ between the two groups; however, the prevalence of coronary artery disease was significantly higher in the obese groups. According to a 2022 study published by Mousaie et al, T1DM is associated with obesity, cardiovascular disease, diabetic neuropathy, retinopathy, and nephropathy, while T2DM is associated with obesity, cardiovascular disease, and nephropathy. In particular, diabetic retinopathy is strongly associated with obesity in T1DM and diabetic neuropathy is strongly associated with obesity in T2DM, which is consistent with the results of this study in terms of diabetic retinopathy and cardiovascular disease.[19]

There are some limitations in this study. The clinical factors associated with obesity, such as physical activity and dietary habits, were not assessed in this study. Additionally, other important parameters related to obesity, including waist circumference and body composition, could not be obtained due to the retrospective nature of the study. The absence of a control group consisting of individuals without T2DM represents another limitation. Finally, not all polymorphisms of MCP-1 were investigated in this analysis. Therefore, a prospective study that corrects for these factors is needed.

Conclusion

In conclusion, this study demonstrates that the non-G allele of MCP-1 2518 A/G polymorphism is significantly associated with obesity in Korean patients with T2DM. Additionally, hypertension, dyslipidemia, and female sex were identified as independent risk factors for obesity in this population. These findings underscore the complex interplay between genetic and metabolic factors in the pathogenesis of obesity, highlighting the need for personalized approaches to obesity management in patients with T2DM. Further studies involving various ethnic groups are required to confirm our results.

Data Sharing Statement

Data may be available from the corresponding author with a reasonable request.

Ethics Declarations

Written informed consent was obtained from all participants. This study was approved by the Institutional Review Board of the Chungbuk National University Hospital (IRB No. 2017-10-009-009). The current study was conducted according the guidelines administered by the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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