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Effect of smoking and obesity on the association between HMGCR rs12654264 and type 2 diabetes in a Korean population

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Research Article

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Abstract

Methods

A total of 4,239 participants were included. Fasting blood glucose (FBG) and lipid levels were measured after a 12-hour fast. Diabetes was defined as FBG ≥ 126 mg/dL, a prior diagnosis of diabetes, or use of antidiabetic medication. Associations were evaluated using linear regression under an additive genetic model and logistic regression under a recessive model. Interaction terms were included to assess effect modification by smoking and waist circumference.

Results

The rs12654264 SNP was associated with FBG and LDL-C levels. After adjustment for age, sex, and BMI, healthy men with the TA/AA genotype had an increased risk of diabetes compared with those with the TT genotype (OR 1.50; 95% CI 0.98–2.29). The association was stronger among male non-smokers and light smokers (OR 3.59; 95% CI 1.37–9.39; p = 0.0094) than among heavy or former smokers. The interaction between rs12654264 and smoking was significant (P for interaction = 0.0141). A stronger association was also observed in men with waist circumference < 86 cm (OR 9.12; 95% CI 1.21–68.6).

Conclusions

The HMGCR rs12654264 variant was associated with type 2 diabetes in Korean men. This association was stronger among lean individuals and non-smokers or light smokers, suggesting potential gene–environment interaction.

Introduction

Fasting blood glucose is a primary indicator used to diagnose diabetes [1]. A meta-analysis of randomized controlled trials reported that statin therapy, compared with usual care or placebo, increased the risk of type 2 diabetes mellitus (T2DM) [2]. HMGCR gene polymorphisms have been investigated as genetic proxies for statin-induced HMGCR inhibition [3]. Low-density lipoprotein cholesterol (LDL-C) has been associated with the rs12654264 SNP in the HMG-CoA reductase (HMGCR) gene [4, 5]. A recent study reported a significant association between elevated fasting glucose and genetically proxied inhibition of HMGCR [6]. Another study showed that HMGCR polymorphisms were associated with diabetes risk in patients with premature triple-vessel disease [7]. In addition, the TT genotype of rs12654264 was associated with a lower risk of T2DM [8].

Genetic and environmental factors, as well as their interactions, contribute to the development of T2DM [8–10]. Smoking is an established risk factor for type 2 diabetes [11]. A recent study suggested that smoking may modify the effect of a glucagon-related genetic variant on type 2 diabetes risk [12]. However, previous studies have not examined whether smoking status modifies the association between rs12654264 and type 2 diabetes. Therefore, the aim of this study was to investigate whether smoking influences the association between the HMGCR rs12654264 polymorphism and type 2 diabetes in a

Korean population. We also evaluated whether this association differed according to waist circumference.

Methods

Study population

A total of 4,294 participants underwent general health examinations at university hospital health promotion centers [13]. As part of the Korean Cancer Prevention Study-II (KCPS-II) Biobank, biological samples for DNA extraction were prospectively collected between 2004 and 2013 [14].

Of the 4,294 participants, 55 were excluded due to missing data on rs12654264 genotype, body mass index (BMI), or fasting blood glucose. The final analytic sample included 4,239 participants, of whom 1,769 had cardiovascular disease (CVD). The remaining 2,470 participants were classified as healthy. Healthy participants were defined as individuals without cardiovascular disease. Missing data were observed for waist circumference (n = 862), LDL-C (n = 425), and smoking status (n = 301).

All participants provided written informed consent prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Eulji University (approval number: EUIRB2023-072).

Data collection

Trained interviewers administered a standardized questionnaire to collect information on demographics (age and sex), medical history, medication use, and smoking status (never, former, or current smoker). Participants were classified as current smokers if they were smoking at the time of examination, former smokers if they had smoked previously but had quit, and never smokers if they had never smoked.

Height and weight were measured with participants wearing light clothing and no shoes.

Peripheral venous blood samples were collected after a 12-hour overnight fast to measure fasting blood glucose (FBG), total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Samples were stored at − 70°C until analysis. Biochemical measurements were performed using a Hitachi 7600 analyzer (Hitachi Ltd., Tokyo, Japan). Detailed phenotype data have been described previously [13, 14].

Genotyping assays

The HMGCR rs12654264 SNP was genotyped using a TaqMan allelic discrimination assay [15]. SNPs with a concordance rate > 99% in duplicate samples and a genotype call rate > 98% were included in the analysis.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Most statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Linear regression under an additive genetic model was used to assess the association between rs12654264 and fasting blood glucose levels, adjusting for age and sex. Logistic regression under a recessive genetic model was used to evaluate the association between rs12654264 and diabetes. Waist circumference and BMI were dichotomized at their median values.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the association between rs12654264 and diabetes. Diabetes was defined as a fasting blood glucose level ≥ 126 mg/dL, a prior diagnosis of diabetes, or the use of antidiabetic medication. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

The mean age was 51.9 years for men and 52.7 years for women. Overall, 10.7% of participants had diabetes. The mean age was 57.3 years among participants with diabetes and 51.6 years among those without diabetes. Compared with participants without diabetes, those with diabetes had higher BMI and waist circumference. They also had a higher proportion of men and a family history of diabetes (Table 1).

After adjustment for age and sex, the associations between rs12654264 and fasting blood glucose (FBG) levels are shown in Table 2. The rs12654264 SNP in the HMGCR gene was associated with FBG and LDL-C levels (effect per allele: 0.999 mg/dL, $p = 0.0354$ for FBG; −2.864 mg/dL, $p < 0.0001$ for LDL-C). Among healthy participants, rs12654264 was associated with FBG and LDL-C levels (effect per allele: 1.260 mg/dL, $p = 0.0211$ for FBG; −3.603 mg/dL, $p < 0.0001$ for LDL-C).

The association between rs12654264 and diabetes is presented in Table 3. After adjustment for age, sex, and BMI, healthy men with the TA/AA genotype had a 1.37-fold higher risk of diabetes compared with those with the TT genotype (OR 1.37; 95% CI 0.96–1.98). In men overall, the association was stronger (OR 1.50; 95% CI 0.98–2.29), whereas no significant association was observed in women (OR 1.06; 95% CI 0.53–2.14).

Stratified analyses by smoking status in men are shown in Table 4. The association between rs12654264 and diabetes was stronger among male non-smokers and light smokers (OR 3.59; 95% CI 1.37–9.39; $p = 0.0094$) than among heavy smokers ($p = 0.2928$) or former smokers ($p = 0.1099$). Stratified analyses by BMI and waist circumference (WC) are also shown in Table 4. Among men with WC < 86 cm, the association between rs12654264 and diabetes was stronger (OR 9.12; 95% CI 1.21–68.6; $p = 0.0317$) than among those with WC ≥ 86 cm ($p = 0.6197$).

Table 5 presents age-adjusted odds ratios for diabetes according to rs12654264 genotype across smoking categories among Korean men. Heavy smokers with the TT genotype had an OR of 3.25 (95% CI 1.44–7.32) compared with non-, former, or light smokers with the TA/AA genotype (P for interaction = 0.0141).

Discussion

The rs12654264 SNP in the HMGCR gene was associated with serum glucose levels in this cohort of 4,239 individuals. Previous studies have reported that T2DM is associated with genetic variants in the HMGCR gene [16]. A recent Mendelian randomization study showed that genetically proxied inhibition of HMGCR was associated with lower blood pressure and higher fasting glucose levels [6]. A meta-analysis of randomized controlled trials reported that statin therapy increased the risk of developing T2DM compared with placebo or usual care [2]. Another study examined rs17238484 and rs12916, two SNPs in the HMGCR gene, as genetic proxies for statin-induced HMGCR inhibition and found that both statin therapy and common HMGCR variants were associated with weight gain and an increased risk of T2DM [3]. In addition, HMGCR variants have been associated with T2DM and cardiovascular disease in multi-ethnic populations [17]. In the present study, the TT genotype of rs12654264 was associated with lower fasting glucose levels compared with the AA genotype.

Type 2 diabetes is strongly associated with smoking [11, 18, 19]. In this study, the association between rs12654264 and diabetes was stronger among non-smokers and light smokers than among heavy smokers. Previous studies have suggested that smoking influences fasting glucose levels [12, 20]. Smoking has also been reported to modify the effect of glucagon-related genetic variants on T2DM risk [12]. These findings support the possibility of gene–environment interaction between HMGCR variants and smoking.

The rs12654264 SNP has been associated with LDL-C levels in genome-wide association studies conducted in East Asian populations [4]. A Chinese study also reported an association between rs12654264 and LDL-C levels [5]. Similarly, a Korean study found a significant association between rs12654264 and LDL-C levels [21]. However, no significant association between rs12654264 and plasma lipid levels was observed in a Czech population [22]. In the present study, rs12654264 was associated with LDL-C levels, consistent with findings from East Asian cohorts.

Previous studies have reported associations between HMGCR variants and obesity-related traits, including waist circumference, body weight, and BMI [3, 8, 23]. Body weight is a major risk factor for T2DM and is closely related to insulin resistance [3]. This may partly explain the increased risk of T2DM observed with statin therapy. A recent study in children and adolescents with autism spectrum disorder also reported associations between HMGCR polymorphisms, lipid metabolism, and obesity-related phenotypes [24].

In our study, the association between rs12654264 and diabetes was stronger in men than in women among healthy participants. A Chinese study reported that rs12654264 was associated with LDL-C

levels and that the association was stronger in women than in men [25]. Sex-specific effects of HMGCR variants on lipid traits have also been reported in other populations [26]. These findings suggest potential sex-specific genetic effects of HMGCR variants.

HMG-CoA reductase (HMGCR), located on chromosome 5q13.3, is the rate-limiting enzyme in cholesterol biosynthesis and catalyzes the conversion of HMG-CoA to mevalonate [27]. Mevalonate is a precursor of cholesterol and several nonsterol isoprenoid compounds, including dolichol, ubiquinone, and isopentenyl tRNA [28]. In 5,414 participants from the Malmö Diet and Cancer Study, rs12654264 was associated with LDL-C levels [29]. The frequency of the rs12654264 A allele varies across populations: 61.7% in Europeans, 68.0% in Africans, and 46.1% in East Asians, according to HapMap data.

This study has several limitations. Baseline characteristics, including the prevalence of diabetes, cardiovascular disease, and smoking, differed by sex. We were unable to distinguish between types of diabetes; however, type 1 diabetes accounts for approximately 1% of diabetes cases in Korea [30]. In addition, a large number of CVD patients were included because the case–control design of the KCPS-II dataset was originally established to collect CVD cases [14]. Therefore, we conducted subgroup analyses in participants without cardiovascular disease to examine the association between rs12654264 and diabetes.

Conclusion

Genetic backgrounds may differ across populations. In this Korean cohort, the HMGCR rs12654264 variant was associated with type 2 diabetes, particularly among lean men and male non-smokers or light smokers. These findings suggest a potential gene–environment interaction between HMGCR and smoking in the development of type 2 diabetes.

Declarations

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The authors have no acknowledgements to declare.

Authors' contributions

JWS (Sull) conceived and designed the study, acquired the data, performed the analysis, interpreted the results, and drafted and revised the manuscript.

JWS (Shin) critically revised the manuscript.

SHJ conceived and designed the study, acquired the data, performed the analysis, interpreted the results, and critically revised the manuscript.

All authors read and approved the final manuscript.

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The funding body had no role in the design of the study; collection, analysis, and interpretation of data; or in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. Ethical approval was granted by the Institutional Review Board of Eulji University (approval number: EUIRB2023-072).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 General characteristics of the study population

Subjects		Diabetes*	Non-diabetes	P value
N		455	3784	
		Mean ± SD	Mean ± SD	
Age, year		57.3±9.5	51.6±10.1	<0.0001
Weight, kg		69.7±10.4	67.2±11.1	<0.0001
Waist circumference, cm		88.5±8.4	83.6±8.9	<0.0001
Body mass index, kg/m^2		25.3±3.0	24.3±2.9	<0.0001
Systolic blood pressure, mmHg		126.0±14.8	121.4±14.4	<0.0001
LDL-C, mg/dL		111.1±36.6	117.4±31.0	<0.0001
HDL-C, mg/dL		47.6±10.4	51.3±11.7	<0.0001
Triglyceride, mg/dL		180.3±136.6	139.2±89.5	<0.0001
		%	%	
Male		76.7	67.0	<0.0001
Smoking status	Ex	33.6	27.9	0.0372
	Current	26.3	27.0	
Cardiovascular disease		59.8	39.6	<0.0001
Family history of diabetes		25.7	13.2	<0.0001

Diabetes was defined as fasting serum glucose ≥ 126 mg/dL, previous diagnosis of diabetes, or use of antidiabetic medication.

Abbreviations: SD, standard deviation; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Table 2 Association between the rs12654264 in the HMGCR gene and fasting blood-sugar and lipids levels based on a linear regression model

	Genotypes				
Phenotypes	TT	TA	AA	Effect (mg/dL)	*P*-value
	Mean±SD	Mean±SD	Mean±SD		
All subjects	(N=1170)	(N=2058)	(N=1011)		
Fasting blood sugar, mg/dL	96.6±21.5	96.6±21.8	98.4±25.3	0.999	0.0354
Body mass index, kg/m^2	24.4±3.0	24.4±2.9	24.5±3.0	0.091	0.1378
LDL cholesterol, mg/dL	119.5±33.0	116.7±31.5	113.8±30.2	-2.864	<0.0001
HDL cholesterol, mg/dL	50.8±11.2	51.0±11.9	51.0±11.5	-0.011	0.9628
Triglyceride, mg/dL	146.5±91.4	141.1±92.3	145.4±109.4	-0.243	0.9049
	%	%	%		
Cardiovascular disease	41.6	41.7	41.8		0.9973
Diabetes	11.4	10.7	10.2		0.6635
Healthy subjects	(N=681)	(N=1199)	(N=590)		
Fasting blood sugar, mg/dL	93.9±18.8	94.1±18.4	96.3±23.1	1.260	0.0211
Body mass index, kg/m^2	24.1±2.8	24.1±3.0	24.0±2.9	-0.016	0.8370
LDL cholesterol, mg/dL	123.0±31.0	118.9±29.7	115.6±29.4	-3.603	<0.0001
HDL cholesterol, mg/dL	51.7±11.6	52.1±12.6	52.0±12.5	0.064	0.8435
Triglyceride, mg/dL	137.6±79.6	133.4±76.9	134.4±96.1	-1.273	0.5678
	%	%	%		
Diabetes	8.3	7.7	6.2		0.3099

Effect sizes (β) and corresponding p values were estimated using multiple linear regression under an additive genetic model adjusted for age and sex. P values for cardiovascular disease and diabetes were calculated using the chi-square test. *p < 0.05 was considered statistically significant.*

Table 3 Odds ratios (OR) of the polymorphic rs12654264 HMGCR genotypes for diabetesin the population

		Normal	Diabetes [a]				
				Model 1		Model 2	
Subjects	Genotype	*N* (%)	*N* (%)	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
All	TT	1051 (27.8)	119(26.1)	1.00 (reference)		1.00 (reference)	
(n = 4,239)	TA /AA	2733 (72.2)	336(73.9)	1.12(0.89-1.40)	0.3423	1.11(0.88-1.39)	0.3845
Men	TT	724 (28.6)	87(24.9)	1.00 (reference)		1.00 (reference)	
	TA/AA	1811 (71.4)	262(75.1)	1.21(0.93-1.57)	0.1553	1.21(0.93-1.57)	0.1583
Women	TT	327 (26.2)	32(30.2)	1.00 (reference)		1.00 (reference)	
	TA/AA	922 (73.8)	74(69.8)	0.90(0.58-1.41)	0.6402	0.82(0.52-1.30)	0.3991
All Healthy	TT	639 (27.9)	42(22.9)	1.00 (reference)		1.00 (reference)	
(n = 2,470)	TA /AA	1648 (72.1)	141(77.1)	1.38(0.96-1.98)	0.0830	1.37(0.96-1.98)	0.0863
Men	TT	418 (28.6)	30(21.7)	1.00 (reference)		1.00 (reference)	
	TA/AA	1044 (71.4)	108(78.3)	1.49(0.97-2.27)	0.0669	1.50(0.98-2.29)	0.0637
Women	TT	221 (26.8)	12(26.7)	1.00 (reference)		1.00 (reference)	
	TA/AA	604 (73.2)	33(73.3)	1.14(0.57-2.29)	0.7096	1.06(0.53-2.14)	0.8731

Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, and body mass index (BMI).
[a] Diabetes was defined as fasting serum glucose ≥ 126 mg/dL, previous diagnosis of diabetes, or use of antidiabetic medication.

Abbreviations: CI, confidence interval; BMI, body mass index.

Table 4 Odds ratios (OR) of polymorphic rs12654264 HMGCR genotypes for diabetes[a] in Healthy Korean men (n = 1,600)

		Normal	Diabetes*		
Subjects	Genotype	*N* (%)	*N* (%)	OR (95% CI)	*P*-value
Non smokers or Light smokers (1-19/day)	TT	174(30.5)	5(11.9)	1.00 (reference)	
	TA/AA	397(69.5)	37(88.1)	3.59(1.37-9.39)	0.0094
Ex smokers	TT	148(27.9)	12(19.7)	1.00 (reference)	
	TA/AA	382(72.1)	49(80.3)	1.72(0.88-3.36)	0.1099
Heavy smokers (≥20/day)	TT	86(27.4)	11(34.4)	1.00 (reference)	
	TA/AA	228(72.6)	21(65.6)	0.66(0.30-1.44)	0.2928
Waist circumference < 86	TT	125(29.9)	1(4.4)	1.00 (reference)	
	TA/AA	293(70.1)	22(95.7)	9.12(1.21-68.6)	0.0317
Waist circumference ≥ 86	TT	123(28.7)	15(26.3)	1.00 (reference)	
	TA/AA	305(71.3)	42(73.7)	1.17(0.63-2.20)	0.6197
BMI < 24.60	TT	209(28.1)	10(17.2)	1.00 (reference)	
	TA/AA	534(71.9)	48(82.8)	1.89(0.93-3.81)	0.0773
BMI ≥ 24.60	TT	209(29.1)	20(25.0)	1.00 (reference)	
	TA/AA	510(70.9)	60(75.0)	1.30(0.76-2.23)	0.3410

[a] Adjusted for age and body mass index * Diabetes were defined as fasting serum glucose ≥126 mg/dL or medication or previously diagnosed.

Abbreviations: CI, confidence interval

Table 5 Age-adjusted odds ratios (OR) for diabetes[a] according to HMGCR (rs12654264) genotypes in strata of smoking statusin Healthy Korean men (n = 1,600)

Subjects	No. of subjects by genotypes	OR (95% CI)		
		TT	TA/AA	*P* for interaction
Smoking status				0.0141
Non/Ex/Light smokers	339/865	1.00 (reference)	2.23 (1.30-3.84)	
Heavy smokers	97/346	3.25 (1.44-7.32)	2.21 (1.13-4.35)	

[a] Adjusted for age

Abbreviations: CI, confidence interval