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Sex Differences in the Effects of *CDKAL1* Variants on Glycemic Control in Diabetic Patients: Findings from the Korean Genome and Epidemiology Study

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Background: Using long-term data from the Korean Genome and Epidemiology Study, we defined poor glycemic control and investigated possible risk factors, including variants related to type 2 diabetes mellitus (T2DM). In addition, we evaluated interaction effects among risk factors for poor glycemic control.

Methods: Among 436 subjects with newly diagnosed diabetes, poor glycemic control was defined based on glycosylated hemoglobin trajectory patterns by group-based trajectory modeling. For the variants related to T2DM, genetic risk scores (GRSs) were calculated and divided into quartiles. Risk factors for poor glycemic control were assessed using a logistic regression model.

Results: Of the subjects, 43% were in the poor-glycemic-control group. Body mass index (BMI) and triglyceride (TG) were associated with poor glycemic control. The risk for poor glycemic control increased by 11.0% per 1 kg/m^2 increase in BMI and by 3.0% per 10 mg/dL increase in TG. The risk for GRS with poor glycemic control was sex-dependent ($P_{interaction}$=0.07), and a relationship by GRS quartiles was found in females but not in males. Moreover, the interaction effect was found to be significant on both additive and multiplicative scales. The interaction effect was evident in the variants of cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like (*CDKAL1*).

Conclusion: Females with risk alleles of variants in *CDKAL1* associated with T2DM had a higher risk for poor glycemic control than males.

Keywords: Diabetes mellitus; Gene-environment interaction; Glycemic control; Sex characteristics

INTRODUCTION

Between 1990 and 2017, the global incidence and prevalence of diabetes increased significantly, by 102.9% (from 11.3 million to 22.9 million) and 129.7% (from 211.2 million to 476.0 million), respectively [1]. The estimated number of people with diabetes in South Korea increased from 3.2 million in 2010 to 4.9 million in 2018 [2]. A high body mass index (BMI) and poor environmental or behavioral factors reportedly contribute to the burden of diabetes [1]. Therefore, the prevention and management of diabetes are major public-health issues.

In diabetic patients, glycemic control is the major goal of treatment, with the aim of preventing complications such as diabetic retinopathy, diabetic nephropathy, and cardiovascular disease (CVD). According to a fact sheet on diabetes in South Korea, only 28.3% of patients achieve the target level of glycemic control (<6.5% glycosylated hemoglobin [HbA1c]) [2]. Studies in Brazil [3], China [4], and Canada [5] have also re-

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ported high rates of poor glycemic control. Duration of diabetes, family history, BMI, and unhealthy behaviors are reportedly associated with poor glycemic control [4,6-9]. In addition, there are sex disparities in diabetes management [10]. Studies also reported that adiponectin gene (*ADIPQO*) [11] and type 2 deiodinase (*Dio2*) [12] variants are related to glycemic control, and carboxypeptidase A6 (*CPA6*) and pre-mRNA processing factor 31 (*PRPF31*) variants are associated with the response to metformin, the first-line treatment for type 2 diabetes mellitus (T2DM) [13]. Although metabolic, behavioral, and genetic factors are related to glycemic control, additional studies are needed considering the ethnic-specific effects of variants and socio-environmental differences. In addition, interactions with genetic factors need to be evaluated to elucidate disease progression. A recent Korean meta-analysis identified 23 variants related to T2DM using the genome-wide association study (GWAS) catalog data [14].

Therefore, using long-term cohort data, we investigated risk factors, including 23 genetic variants related to T2DM, for poor glycemic control in newly diagnosed diabetic patients. In addition, we assessed interaction effects of genetic determinants on poor glycemic control.

METHODS

Data sources and study subjects
This study used data from the community-based cohort of the Korean Genome and Epidemiology Study (KoGES). Detailed information on this cohort has been published [15]. Briefly, to investigate risk factors for chronic diseases among Koreans, a community-based cohort study was started in 2001 to 2002 and involved residents (aged 40 to 69 years) from two communities (Ansung and Ansan) who agreed to participate. A total of 10,030 participants completed the baseline survey (Ansung, a rural region [*n*=5,018] and Ansan, an industrial region [*n*=5,012]). Follow-up data were collected every 2 years and the study is ongoing. The follow-up surveys include questionnaires, anthropometric/biomarker measurements, blood sampling (collected after overnight fasting), and urine tests. This study included data up to the eighth follow-up (conducted in 2017 to 2018; follow-up rate=61.4%).

The data were reconstructed according to the research objective. We included subjects who responded that they had been diagnosed with diabetes by a physician (*n*=1,601). Of them, only newly diagnosed patients with diabetes were in-

cluded during the follow-up period, excluding patients with a history of diabetes in the baseline survey (*n*=896). In addition, subjects with a history of CVD or cancer prior to diagnosis of diabetes were excluded (*n*=803). To define the trajectory pattern of HbA1c, we included subjects who reported a diagnosis of diabetes in the first to fifth follow-up surveys (*n*=542). Finally, we analyzed the data of 436 subjects (228 males and 208 females) after excluding those with insufficient information. The protocol was approved by the Institutional Review Board of Ewha Womans University Hospital (EUMC 2021-03-008). Review board requirement for written informed consent was waived because this study used an anonymous dataset.

Trajectory of HbA1c
Except for the first follow-up (2003 to 2004), HbA1c data were collected in all follow-up surveys. To evaluate the pattern of changes in HbA1c after diagnosis, the survey time point at which the subject responded that they had been diagnosed by a physician was defined as the index time, and survey data at subsequent time points were used for trajectory pattern analysis. The average number of HbA1c measurements was 4.6 ± 1.6.

Based on their pattern of change in Hb1Ac over time, participants were classified into groups using the Proc Traj procedure in SAS software for group-based trajectory modeling [16]. Group-based trajectory modeling is designed to identify clusters of individuals who experience similar changes in an indicator of interest over time. It can specify the number of trajectory groups and different order polynomials for each group. Among the various potential models, reasonable group size (>5%) and Bayesian information criterion (BIC) values are typically used to determine the best-fit model [17]. We calculated the logged Bayes factor ($2*\Delta$BIC) to determine the optimal model [18]. In our data, the BIC values for two (order by each group: linear and linear) and three patterns (order by each group: linear, quadratic, and linear) were −2,959.57 and −2,831.78, respectively. The four-pattern model did not satisfy the group size requirements. Therefore, based on the logged Bayes factor, a three-pattern model was selected instead of a two-pattern model. For the selected model, each individual was assigned to a specific trajectory group based on the highest posterior probability. Sex and age affected the probability of belonging to a particular group, so we included sex and age in the model. The target glycemic control level in diabetic patients is HbA1c <6.5% [2]; the poor-glycemic-control group was defined based on this value.

Risk factors assessment

We evaluated potential risk factors for poor glycemic control including demographic factors, age at the time of diabetes diagnosis, metabolic factors, behavioral factors, and genetic factors. BMI (kg/m²), blood pressure (mm Hg), triglyceride (TG, mg/dL), and high-density lipoprotein cholesterol (HDL-C, mg/dL) were analyzed as metabolic factors, and current smoking and alcohol intake (no alcohol, <15, 15–24.9, and ≥25 g/day) [19] as behavioral factors. Metabolic and behavioral factors were evaluated using data at the time the subject responded that they had been diagnosed with diabetes by a physician (i.e., index time). At each follow-up, antidiabetic drug use was investigated, but detailed information on dose, duration, and type was not collected.

Cho et al. [14] performed a meta-analysis of susceptibility to T2DM using Exom chip KoGES data and the GWAS catalog database; 23 variants were significant. Of the 23 single nucleotide polymorphisms (SNPs), rs10440833, rs4712523, rs7754840, rs-4712524, rs10946398, and rs9295474 in cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like (*CDKAL1*) showed strong linkage ($r^2 ≥ 0.8$) in linkage disequilibrium analysis. Therefore, we considered only rs7754840 of *CDKAL1* in the genetic risk scores (GRSs) calculation. Using the meta-analysis of Cho et al. [14], weighted GRSs were calculated for 18 variants. Depending on the number of minor alleles, 0, 1, and 2 were assigned and SNPs were weighted with the effect sizes derived from the meta-analysis. These were multiplied by (18/sum of the effect size) [20].

Statistical analysis

Results are presented as means with standard deviation or medians with interquartile range for numerical variables, and frequencies with percentage for categorical variables. Differences according to glycemic control group were assessed by *t*-test, Mann–Whitney *U* test, and chi-square test.

As potential risk factors for poor glycemic control, basic characteristics were evaluated by logistic regression model; the results are presented as odds ratios with 95% confidence intervals (95% CIs). Significant risk factors were identified by a stepwise selection method considering basic characteristics except for overlapping variables. Multivariate analysis was performed by adding sex, age, and weighted GRSs to the selected variables. Interaction effects were also evaluated for the variables included in multivariate analysis. Quantitative interactions for poor glycemic control were assessed on additive and multiplicative scales [21]. Additive scales were assessed using

the relative excess risk due to interaction (RERI). We evaluated the interactions with 23 SNPs for poor glycemic control as an additional measure.

A mixed-model analysis was performed to estimate differences in HbA1c according to genotype by sex. A random-intercept model was constructed to include group (i.e., genotype), measurement time point, and the interaction between group and measurement time point as fixed effects, as well as the covariates from the multivariate model. The covariance structure for the model was determined according to low BIC values. The results are presented as least-squares means with 95% CIs. In addition, as the sensitivity analysis, an analysis of those taking antidiabetic drugs at index time was performed.

All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was determined as a value of *P*<0.05 in a two-tailed test.

RESULTS

The HbA1c trajectory was classified into three patterns, and 43% of the subjects (*n*=189; group 2 and group 3) showed a higher than target HbA1c value (HbA1c ≥6.5%); they made up the poor-glycemic-control group. Of them, 6.0% (*n*=26, group 3) showed a persistent deterioration in mean HbA1c during the observation period (Fig. 1).

The basic characteristics of the subjects are listed in Table 1. The average age at the time of diabetes diagnosis was 56.1 years, and 47.7% of the subjects were female. Of the subjects recently diagnosed with diabetes by a physician, about 60.0% had a BMI ≥25.0 kg/m². Of the subjects, 52.4% and 63.3% had a high TG level and low HDL-C level, respectively, but the percentage of diagnosis by a physician was only 14.9%. Furthermore, about 20% of the subjects were current smokers. When compared according to glycemic control group, there were differences in BMI and TG, with higher average value in the poor-glycemic-control group. Antidiabetic drug intake was generally higher in the poor-glycemic-control group during the follow-up period (Supplementary Fig. 1).

BMI and TG were significantly associated with poor glycemic control. The risk for poor glycemic control increased by 11.0% per 1 kg/m² increase in BMI and by 3.0% per 10 mg/dL increase in TG. Those in the highest quartile of GRS had a 1.3-fold (95% CI, 0.7 to 2.3) greater risk for poor glycemic control than those in the lowest quartile, but it was not significant (Table 2). In addition, among the interactions of the risk factors
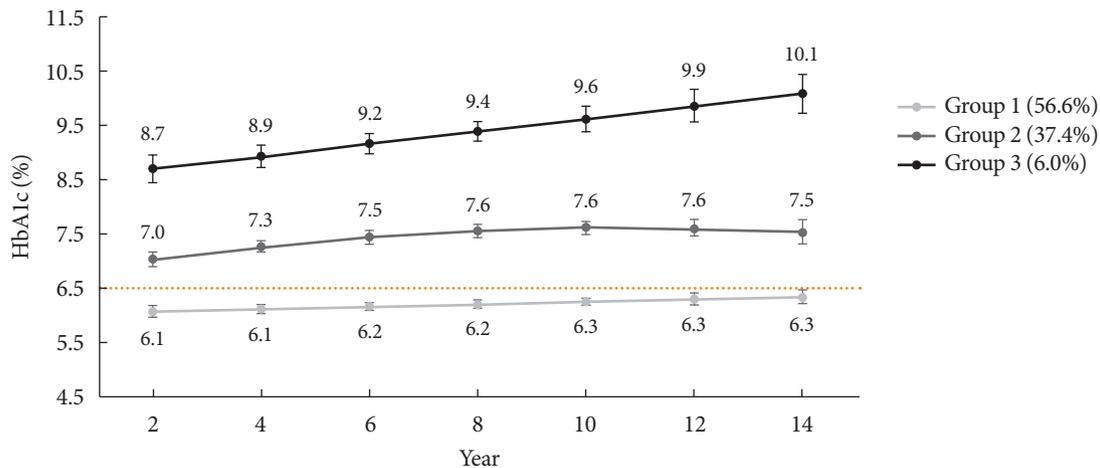
Fig. 1. Trajectories of glycosylated hemoglobin (HbA1c, %) after diabetes diagnosis. Trajectory patterns were identified using group-based trajectory modeling. Solid lines represent estimates and bars represent 95% confidence intervals. Dashed red line indicates that the target HbA1c level was 6.5%.

selected in the multivariate model, that between sex and GRS was a borderline significant (*P*=0.07).

Results for quartiles of weighted GRS and sex interaction for poor glycemic control are shown in Table 3. For poor glycemic control, a relationship by GRS quartiles was found in females but not in males. The quartiles of GRS in females was found to be a synergistic effect for poor glycemic control, irrespective of the interaction scale.

Of the 23 SNPs, rs10440833, rs4712523, rs7754840, rs4712524, rs10946398, and rs9295474 in *CDKAL1* showed an insignificant interaction with sex in terms of the Bonferroni-correction for multiple comparisons (Supplementary Table 1). However, when the associations were stratified on the basis of sex, distinct associations were observed only in females (Supplementary Table 2). The additive interactions of these SNPs were clear in female homozygous carriers of the minor allele (Table 4). Evaluation according to rs7754840 and rs10440833 genotypes showed that the mean HbA1c values tended to be higher in the presence of risk alleles, and the average values differed significantly according to genotype (Fig. 2). When evaluated in subjects taking antidiabetic drugs at the time of index assessment, the risk for poor glycemic control in females differed according to GRS level. In females, the quartiles of GRS was linked to an increased risk for poor glycemic control (data not shown).

DISCUSSION

Using long-term observational data, we evaluated poor glyce-

mic control as defined by the HbA1c trajectory. Our study showed genetic predisposition to T2DM to be related to glycemic control in diabetic patients and to differ by sex. In addition, its interaction effect was evident in the variants of *CDKAL1*.

CDKAL1 is reportedly linked to predisposition to T2DM through GWASs in various ethnicities [14]. The C allele of the *CDKAL1* rs7754840 G/C polymorphism was significantly associated with an increased risk for T2DM based on a meta-analysis of 32 independent studies [22]. A recent GWAS based on six independent cohorts also found that *CDKAL1* variants were associated with beta-cell glucose sensitivity [23]. *CDKAL1* has enzymatic activity, and *CDKAL1* may be related to pancreatic beta-cell function and insulin resistance [22].

Our study showed that *CDKAL1* variants were associated with poor glycemic control, and the association was stronger in females than in males. Indeed, sex differences were found in the association between rs7756992 and rs9465871 in *CDKAL1* and T2DM, and the association was stronger in females than in males [24]. A study on the Yup'ik people from Southwest Alaska [25] showed that the association between rs7754840 in *CDKAL1* and HbA1c was significant in females but not in males. In a meta-analysis, sex contributed to the heterogeneity of the association between rs7754840 in *CDKAL1* and T2DM [26]. However, a study in Taiwan found no sex difference in the association between rs10946398 of *CDKAL1* and T2DM [27]. Although genetic variation was not taken into account, the Multi-factorial Intervention in type 2 Diabetes in Italy (MIND. IT) study found that diabetic females had worse glucose con-

Table 1. Basic characteristics of the subjects

Characteristic	Number	Total ($n=436$)	Group 1 ($n=247$, 56.6%)	Group2+3 ($n=189$, 43.4%)	P value
Female sex	436	208 (47.7)	111 (44.9)	97 (51.3)	0.186
Age, yr	436	56.1±8.7	56.7±8.5	55.4±8.9	0.134
Rural region	436	228 (52.3)	126 (51.0)	102 (54.0)	0.540
Educational level					0.815
Less than middle-school graduate	434	242 (55.8)	139 (56.5)	103 (54.8)	
Graduated high school		134 (30.9)	73 (29.7)	61 (32.5)	
Some college or higher		58 (13.4)	34 (13.8)	24 (12.8)	
BMI, kg/m^2	434	25.8±3.1	25.3±3.1	26.5±2.9	<0.001
BMI ≥25.0 kg/m^2	434	259 (59.7)	130 (52.6)	129 (69.0)	0.001
TG, mg/dL	435	155 (110–223)	146.5 (107–195)	175 (119–257)	0.001
TG ≥150 mg/dL	435	228 (52.4)	118 (48.0)	110 (58.2)	0.034
HDL-C, mg/dL	436	41.8±9.6	42.4±10.4	41.0±8.5	0.117
Low HDL-C (<40 mg/dL for male, <50 mg/dL for female)	436	276 (63.3)	148 (59.9)	128 (67.7)	0.094
Lipidemia diagnosed by a physician	436	65 (14.9)	39 (15.8)	26 (13.8)	0.555
SBP, mm Hg	436	121.3±15.0	121.4±15.3	121.1±14.6	0.835
DBP, mm Hg	436	79.3±9.3	79.0±9.0	79.8±9.5	0.344
SBP/DBP ≥130/85 mm Hg	436	170 (39.0)	94 (38.1)	76 (40.2)	0.648
HTN diagnosed by a physician	436	195 (44.7)	118 (47.8)	77 (40.7)	0.143
Current smoking	436	95 (21.8)	52 (21.1)	43 (22.8)	0.670
Alcohol intake, g/day					0.041
Nondrinker	434	215 (49.5)	107 (43.7)	108 (57.1)	
<15		113 (26.0)	71 (29.0)	42 (22.2)	
15–24		29 (6.7)	20 (8.2)	9 (4.8)	
≥25		77 (17.7)	47 (19.2)	30 (15.9)	
Unweighted GRS	396	9.9±2.7	9.9±2.8	9.8±2.6	0.808
Weighted GRS	396	9.4±2.8	9.4±2.8	9.5±2.7	0.870
Q1	396	99 (25.0)	61 (26.4)	38 (23.0)	0.876
Q2		100 (25.3)	56 (24.2)	44 (26.7)	
Q3		98 (24.7)	57 (24.7)	41 (24.9)	
Q4		99 (25.0)	57 (24.7)	42 (25.4)	

Values are presented as number (%), mean±standard deviation, or median (interquartile range).
BMI, body mass index; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; GRS, genetic risk score.

trol and CVD risk factor control than diabetic males [10]. In this regard, X-chromosome-based gene-gene interactions, sex hormones, and sex-specific lifestyle factors may be associated with disease risk [26,28]. It has been suggested that differences in BMI by sex may contribute to the progression of T2DM [27]. In this study, the mean BMI of males and females did not significantly different (Supplementary Table 3), and BMI had

an independent effect on poor glycemic control. However, studies evaluating the interactions of genetic determinants with sex for poor glycemic control are lacking, which hampers comparisons.

Among six *CDKAL1* variants, rs7754840 and four others (rs4712523, rs4712524, rs9295474, and rs10946398) were in complete linkage ($r^2=1.0$) and rs10440833 was in strong link-

Table 2. Risk factors related to poor glycemic control (groups 2 and 3)

Variable	OR (95% CI)		
	Univariate model	Multivariate model 1	Multivariate model 2
Sex (female vs. male)	1.29 (0.88–1.89)	1.53 (0.98–2.39)	1.53 (0.98–2.40)
Age, yr	0.98 (0.96–1.01)	0.99 (0.97–1.02)	0.99 (0.97–1.02)
Rural region	1.13 (0.77–1.65)		
Educational level			
Less than middle-school graduate	Reference		
Graduated high school	1.13 (0.74–1.73)		
Some college or higher	0.95 (0.53–1.70)		
BMI, kg/m^2	1.14 (1.06–1.21)	1.11 (1.03–1.19)	1.11 (1.03–1.19)
BMI ≥25.0 kg/m^2	2.00 (1.34–2.98)		
TG per 10 mg/dL	1.03 (1.02–1.05)	1.03 (1.01–1.05)	1.03 (1.01–1.05)
TG ≥150 mg/dL	1.51 (1.03–2.21)		
HDL-C, mg/dL	0.99 (0.97–1.01)		
Low HDL-C (<40 mg/dL for male, <50 mg/dL for female)	1.40 (0.94–2.09)		
Lipidemia diagnosed by a physician	0.85 (0.50–1.46)		
SBP, mm Hg	1.00 (0.99–1.01)		
DBP, mm Hg	1.01 (0.99–1.03)		
SBP/DBP ≥130/85 mm Hg	1.10 (0.74–1.61)		
HTN diagnosed by a physician	0.75 (0.51–1.10)		
Current smoking	1.10 (0.70–1.75)		
Alcohol intake			
Nondrinker, g/day	Reference		
<15	0.59 (0.37–0.93)		
15–24	0.45 (0.19–1.02)		
≥25	0.63 (0.37–1.08)		
Unweighted GRS	0.99 (0.92–1.07)		
Weighted GRS	1.01 (0.94–1.08)	1.01 (0.94–1.09)	
Q1	Reference		Reference
Q2	1.26 (0.72–2.22)		1.36 (0.75–2.44)
Q3	1.16 (0.65–2.04)		1.21 (0.67–2.20)
Q4	1.18 (0.67–2.09)		1.27 (0.70–2.32)
Trend	1.04 (0.87–1.25)		1.06 (0.88–1.28)

Groups 2 and 3 were defined as poor glycemic control as the outcome of interest.
OR, odds ratio; CI, confidence interval; BMI, body mass index; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; GRS, genetic risk score.

age (r^2=0.8). This strong linkage was also detected in Han Chinese and British populations in the GWAS catalog. Therefore, females with a risk allele in any of the six variants may have difficulty controlling their glucose levels. These findings need to be confirmed by further research.

During the observation period, levels of HbA1c were high in the poor-glycemic-control group, despite the high rate of antidiabetic drug use (Supplementary Fig. 1). The therapeutic response can vary depending on genotype. The therapeutic response has been evaluated according to variants in transcription factor 7-like 2 (*TCF7L2*) [29], *CDKAL1* [30], *CPA6*, and *PRPF31* [13]. One study evaluated sulphonylurea treatment in

Table 3. Interaction effects of quartiles of weighted GRS and sex on poor glycemic control (groups 2 and 3)

	Quartiles of weighted GRS				Within strata of sex		
	Q1	Q2	Q3	Q4	Q2 vs. Q1	Q3 vs. Q1	Q4 vs. Q1
Male							
No. with/without outcome	25/28	20/34	15/31	22/36			
OR (95% CI)	Reference	0.64 (0.29–1.44)	0.57 (0.24–1.36)	0.72 (0.32–1.62)	0.64 (0.29–1.44)	0.57 (0.24–1.36)	0.72 (0.32–1.62)
Female							
No. with/without outcome	13/33	24/22	26/26	20/21			
OR (95% CI)	0.52 (0.22–1.25)	1.66 (0.72–3.84)	1.37 (0.61–3.09)	1.28 (0.54–3.01)	3.18 (1.31–7.70)	2.62 (1.11–6.22)	2.44 (0.98–6.07)
Female vs. male, OR (95% CI)	0.52 (0.22–1.25)	2.59 (1.11–6.06)	2.40 (1.00–5.76)	1.78 (0.75–4.25)			
Measure of interaction on additive scale, RERI[a] (95% CI)		1.50 (0.33–2.67)	1.28 (0.33–2.23)	1.04 (0.06–2.01)			
Measure of interaction on multiplicative scale, ratio of ORs (95% CI)		4.95 (1.49–16.48)	4.58 (1.35–15.57)	3.41 (1.01–11.51)			

Groups 2 and 3 were defined as poor glycemic control as the outcome of interest. "No. with outcome" represents the number of subjects in the poor glycemic control group, while the remaining subjects are represented as "No. without outcome." OR and 95% CI were estimated after adjusting for age at diagnosis of diabetes, body mass index, and triglycerides measured at follow-up at the time of reporting a diagnosis of diabetes. GRS, genetic risk score; OR, odds ratio; CI, confidence interval; RERI, relative excess risk due to interaction.
[a]If the 95% CIs of RERI do not include 0, then there is an interaction.

Table 4. Additive interaction effects of SNPs and sex on poor glycemic control (groups 2 and 3)

SNP	Gene	Minor allele	MAF	Sex/RERI	OR (95% CI)		
					Major-allele homozygotes	Heterozygotes	Minor-allele homozygotes
rs4712523	*CDKAL1*	G	0.491	Male	Reference	0.98 (0.48 to 2.02)	1.35 (0.59 to 3.09)
				Female	0.68 (0.27 to 1.73)	1.54 (0.73 to 3.28)	3.31 (1.45 to 7.54)
				RERI[a]		0.88 (−0.07 to 1.83)	2.28 (0.04 to 4.51)
rs4712524	*CDKAL1*	G	0.481	Male	Reference	1.36 (0.67 to 2.77)	1.44 (0.63 to 3.29)
				Female	0.77 (0.31 to 1.93)	1.89 (0.90 to 3.99)	3.94 (1.75 to 8.89)
				RERI[a]		0.76 (−0.43 to 1.94)	2.73 (0.06 to 5.40)
rs7754840	*CDKAL1*	C	0.481	Male	Reference	1.36 (0.67 to 2.77)	1.44 (0.63 to 3.29)
				Female	0.77 (0.31 to 1.93)	1.89 (0.90 to 3.99)	3.94 (1.75 to 8.89)
				RERI[a]		0.76 (−0.43 to 1.94)	2.73 (0.06 to 5.40)
rs9295474	*CDKAL1*	G	0.493	Male	Reference	0.97 (0.47 to 1.99)	1.19 (0.52 to 2.73)
				Female	0.65 (0.26 to 1.66)	1.48 (0.70 to 3.15)	3.18 (1.39 to 7.24)
				RERI[a]		0.99 (0.03 to 1.95)	2.33 (0.18 to 4.48)
rs10440833	*CDKAL1*	A	0.467	Male	Reference	1.33 (0.67 to 2.65)	1.27 (0.57 to 2.87)
				Female	0.76 (0.32 to 1.82)	2.05 (1.00 to 4.18)	3.56 (1.57 to 8.04)
				RERI[a]		0.96 (−0.24 to 2.16)	2.52 (0.03 to 4.98)
rs10946398	*CDKAL1*	C	0.481	Male	Reference	1.36 (0.67 to 2.77)	1.44 (0.63 to 3.29)
				Female	0.77 (0.31 to 1.93)	1.89 (0.90 to 3.99)	3.94 (1.75 to 8.89)
				RERI[a]		0.76 (−0.43 to 1.94)	2.73 (0.06 to 5.40)

Groups 2 and 3 were defined as poor glycemic control as the outcome of interest. OR and 95% CI were estimated after adjusting for age at diagnosis of diabetes, body mass index, and triglycerides measured at follow-up at the time of reporting a diagnosis of diabetes.
SNP, single nucleotide polymorphism; MAF, minor allele frequency; RERI, relative excess risk due to interaction; OR, odds ratio; CI, confidence interval.
[a]If the 95% CIs of RERI do not include 0, then there is an interaction.
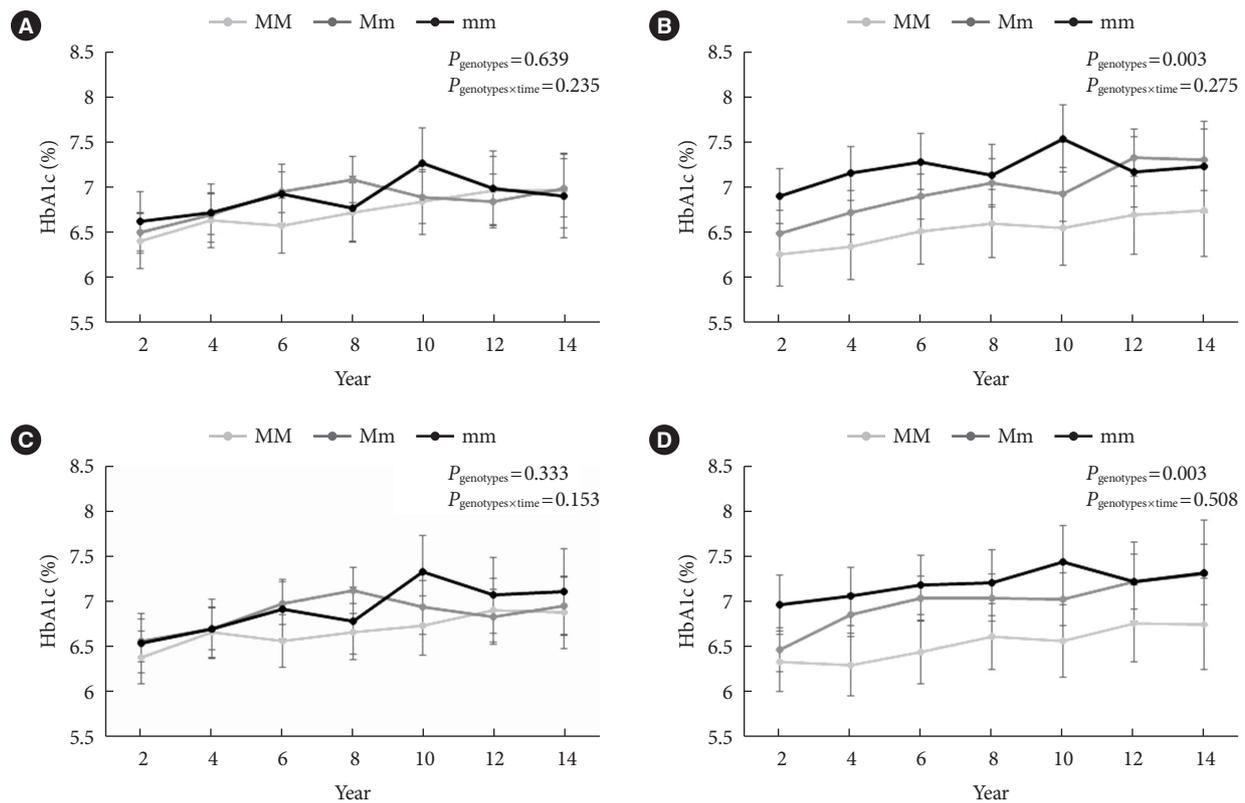
Fig. 2. Changes in average glycosylated hemoglobin (HbA1c, %) after diabetes diagnosis according to single nucleotide polymorphisms in *CDKAL1* by sex. (A) rs7754840 of *CDKAL1* in male. (B) rs7754840 of *CDKAL1* in female. (C) rs10440833 of *CDKAL1* in male. (D) rs10440833 of *CDKAL1* in female. Values are least-squared means and 95% confidence intervals. Estimates were obtained using a mixed model assuming a random intercept with a compound symmetric structure. The model included genotypes, follow-up time, and interaction between genotypes and follow-up time, age at diagnosis of diabetes, and body mass index and triglycerides as time-varying covariates. In linkage disequilibrium, r^2 of rs7754840 with the other four variants (rs4712523, rs4712524, rs9295474, and rs10946398) was 1.0, while the r^2 value with rs10440833 was 0.8 (data not shown). Therefore, only the results for rs7754840 and rs10440833 are presented. MM, major-allele homozygotes; Mm, heterozygotes; mm, minor-allele homozygotes.

subjects who failed to achieve glycemic control on metformin monotherapy, and carriers of the G-allele for *CDKAL1* rs7756992 showed significant reductions in fasting blood glucose [31]. Although we did not evaluate drug use, we defined poor-glycemic-control groups using repeated measurements and identified related genes. Poor glycemic control can have a lasting effect on diabetic complications and prognoses [32]. Regarding diabetes mellitus complications, one study reported that rs10946398 of *CDKAL1* was associated with an increased risk for diabetic retinopathy [33]. Genetic information can assist in selection of the appropriate treatment to improve glycemic control.

Our study found that a high TG level and BMI were independently associated with poor glycemic control. BMI is a major risk factor for T2DM and a high BMI is associated with

poor glycemic control [4]. Considering BMI as a time-varying factor, a high BMI had a persistent effect on a poor HbA1c level (data not shown). Because BMI affects incident CVD, it is necessary to emphasize weight control for glycemic control and prevention of complications in diabetic patients. Hypertriglyceridemia can develop due to poor glycemic control [34]. Although we evaluated TG levels prior to definition of the poor-glycemic-control group, the group had high HbA1c levels at the time of index assessment, which were likely related to TG levels. A high TG level is a risk factor for incident T2DM [35], and can worsen insulin sensitivity, so management of TG has been suggested for glycemic control [36]. In addition, a meta-analysis showed that higher TG levels increased the risk for coronary heart disease in T2DM [37]. In this study, 52.4% and 63.3% of the subjects had a high TG level and low HDL-C

level, respectively, but only 14.9% were aware of dyslipidemia. According to Korean diabetes fact sheets, the rate of target achievement in comprehensive management (HbA1c <6.5%, blood pressure <140/85 mm Hg, and low-density lipoprotein cholesterol <100 mg/dL) was 11.5% [2]. Comorbidities in patients with diabetes can affect the risk for CVD, so comprehensive management, together with glycemic control, is required.

Our study has several strengths and limitations. Our findings were derived from two communities, and so may be generalizable to the general population of South Korea. Inclusion of only newly diagnosed diabetes patients resulted in a small sample size but prevented bias due to the duration of diabetes. Factors related to diabetes management such as self-monitoring of blood glucose, foot care, dietary control, and drug compliance were not considered due to a lack of data. We also did not consider the effects of physical activity and diet on glycemic control because no such data were collected in the follow-up survey. In the GRS calculation, weight information (i.e., coefficients) was estimated from KoGES data including the subjects in this study. There may be an overfitting problem whereby the estimate of the predictive power of the GRS could be inflated [38]. Therefore, these results should be interpreted with caution. Nevertheless, we designed the study with temporal relationships in mind, and relevance was evaluated using repeated measures. We also defined the poor-glycemic-control group based on long-term data, possibly reducing the probability of misclassification bias for poor glycemic control. In addition, our study observed that poor glycemic control can persist. Additive interaction was evaluated in terms of biological interaction, and quantitative relevance was presented. A recent meta-analysis of GWAS data from East Asians reported 301 distinct association signals from 183 loci associated with T2DM [39]. Therefore, it is necessary to expand this study and evaluate these associations in future studies.

CDKAL1 is related to T2DM and its variants can provide insight into the difficulty of glycemic control, particularly in females. For clinical application, further studies should monitor HbA1c levels and drug responses according to *CDKAL1* variant.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2021.0265.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: H.A.L.
Acquisition, analysis, or interpretation of data: H.A.L., H.P., Y.S.H.
Drafting the work or revising: H.A.L., H.P., Y.S.H.
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