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Research Note

Quercetin intake, MATE1 polymorphism, and metabolic syndrome in Korean population: Hallym aging study

Jung Eun Lee[1,2], Hye Won Park[2], Jae Kyung Lee[2], Bo Ram Mok[3], Hae-Jeung Lee[4], Sung-Joon Lee[3,*], and Dong-Hyun Kim[5]

[1]*Department of Food and Nutrition, Seoul National University, Seoul 08826, Korea*
[2]*Department of Food and Nutrition, Sookmyung Women's University, Seoul 04310, Korea*
[3]*Department of Biotechnology, School of Life Sciences & Biotechnology for BK21-PLUS, Korea University, Seoul 02841, Korea*
[4]*Department of Food and Nutrition, College of Bionano Technology, Gachon University, Seongnam, Gyeonggi 13120, Korea*
[5]*Department of Social and Preventive Medicine, Hallym Research Institute of Clinical Epidemiology, College of Medicine, Hallym University, Chuncheon, Gangwon 24252, Korea*

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*Corresponding Author
Tel: +82-2-3290-3029
Fax: +82-2-3290-3653
E-mail: junelee@korea.ac.kr

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Abstract Multidrug and toxic compound extrusion transporter-1 (MATE1) is a quercetin transporter. We examined the associations of quercetin intake and polymorphism of MATE1 in relation to metabolic syndrome (MetS) in Hallym Aging Study. Quercetin intake and the measurements for MetS were assessed in 2004. Six tagging single nucleotide polymorphisms (SNPs) at MATE1 gene were genotyped in 428 Korean adults in 2012. We found a lower prevalence of MetS with quercetin intake; compared to the lowest quartile, odds ratios (ORs, 95% confidence intervals; CIs) were 0.44 (0.24-0.84) for the 3rd quartile. Individuals with the minor allele of MATE1, rs2453589, tended to have a lower prevalence of MetS compared to those with the major allele (OR=0.69; CI=0.36-1.34). However, interactions between quercetin intake and six MATE1 polymorphisms in relation to MetS were not significant (p for interaction $\geq$0.37). In conclusion, intake of quercetin was associated with MetS in Korean populations.

Keywords: quercetin, metabolic syndrome, multidrug and toxic compound extrusion transporter-1, flavonoid

Introduction

Flavonoids are polyphenolic compounds abundant in plant. Given its antioxidant potency, numerous experimental and epidemiologic studies have investigated its beneficial health effects, including reduction in risks of heart disease, inflammation, and cancer (1-3). Flavonols are the most common flavonoids in foods, with quercetin and kaempferol being the most prominent flavonols (1). Onion, kale, broccoli, apples, beans, and berries are major food sources of quercetin in a Western study (4) and onion, yeolmu kimchi, and green tea in a Korean study (5). Multidrug and toxic compound extrusion transporters (MATEs), a group of major secondary active transporters, are found on vacuolar membranes in various plant cells (6). MATEs mediate flavonoid uptake with electrochemical ingradients of protons or sodium ions across membranes (6). MATE1 gene is located in chromosome 17 and its polymorphism has been studied in relation to metabolism of metformin, a glucose-lowering drug (7-9). Quercetin is one of the most abundant flavonoids. Although several experimental studies suggested a potential role of quercetin in the prevention of metabolic disorders (10-12), only a few observation studies have explored this association. Recently, our group have reported that MATE1 has a high affinity for quercetin. We found that the hypolipidemic activity of quercetin and cellular glucose transport was enhanced in HepG2 cells overexpressed with MATE1 gene (13). Given the possible effect of MATE1 transporter on the glucose-related metabolism and the potential role of quercetin in the prevention of metabolic disorder, it may be of interest to examine the associations of quercetin intake, MATE1 gene polymorphism and their interaction in related to metabolic syndrome (MetS). Along with our previous study, we investigated whether quercetin intake and genetic polymorphism related to quercetin intake were associated with MetS.

MetS is a cluster of conditions that occur together and increases risks of cardiovascular disease and diabetes. MetS is defined as having three of the five following components; abdominal obesity, elevated blood pressure, impaired fasting blood glucose, high triglycerides, and low high-density cholesterol levels (14).

To explore the role of quercetin intake and genetic variants of

MATE1 in metabolic disorders, we conducted a cross-sectional study of 428 Korean adults and examined the associations of dietary quercetin intake, genetic polymorphism of MATE1 and its interaction with MetS prevalence.

Materials and Methods

Study subjects and assessment of dietary flavonoid intake Study participants were part of the Hallym Aging Study (HAS), a prospective cohort study of elderly men and women who resided in Chuncheon, Republic of Korea. Study populations were systematically sampled based on the Korean National Census conducted in 2000. HAS cohort was composed of 1,520 men and women (70% aged 65 years) who completed the primary panel survey as well as a second in-depth assessment, but 918 participants out of 1,520 completed face-to-face interviews, and their blood samples were collected in 2004 at baseline. Two more follow-up examinations in 2007 and 2010 were performed. The study design has been described in the previous publication (15).

Among 918 participants (384 men and 534 women), DNAs of 642 participants were extracted at the study center during the second follow-up in 2007. We excluded the following participants; when any of six polymorphisms were not genotyped (*n*=154); participants who did not complete food frequency questionnaire (FFQ) (*n*=11); who had been diagnosed with cancer (*n*=16); or when any components of MetS were not assessed (*n*=33). As a result, 428 participants (186 men and 242 women) were included in this study. All participants provided written informed consent, and the study was approved by the Institutional Review Board at Hallym University.

The dietary intake of participants was assessed using a validated semi-quantitative FFQ in 2004 (16). The amount of quercetin intake per day for each participant was calculated from food items that contained quercetin. Major foods that contributed to quercetin intake in this population were onion, apple, spinach, and strawberry. Energy-adjusted quercetin intake was estimated using the residual method (17). Intakes of red meat, dairy foods, and vegetables and fruits were calculated by summing the intakes of relevant food items that were listed on the FFQs.

Single nucleotide polymorphism (SNP) DNAs of participants were extracted from the buffy coat fraction of centrifuged blood. We selected tagging SNPs of the MATE1 gene by including ±10 kb downstream and upstream from Tagger, which combines the simplicity of pairwise method with the potential efficiency gains of multi-marker approach (18). Common variants with a minor allele frequency of >5% from the Han Chinese in Beijing, China (CHB), and Japanese in Tokyo, Japan (JPT) samples were selected as the reference panel with r^2>0.8 (18). As a result, six tagging SNPs (rs2453589, rs2165894, rs4925026, rs2440161, rs2245639, rs8074784) were selected. The polymorphisms of five SNPs, except rs8074784, were genotyped using Taqman and rs8074784 was genotyped using SNaPshot (Applied Biosystems, Foster City, CA, USA). Observed genotype frequencies of 6 selected SNP was comparable to the genotype frequencious calculated by the Hardy-Weinberg equilibrium (p≥0.09).

Statistical analysis Anthropometric and biochemical measures were assessed in 2004. Waist circumference was measured at the midpoint between the lower costal margin and the level of the iliac crest. Blood samples were collected after ten or more hours of fasting. The systolic blood pressure and diastolic blood pressure were measured using a mercury sphygmomanometer (Riester, Juningen, Germany) and the mean value of two readings was used. Concentrations of fasting plasma glucose, triglyceride, and high-density lipoprotein-cholesterol were measured using an auto-analyzer (Hitachi 747; Hitachi, Tokyo, Japan). The prevalence of MetS was defined as having three of the five following components (14); waist circumference 90 cm for men and 85 cm for women; triglyceride 150 mg/dL or treatment of dyslipidemia; HDL-cholesterol <40 mg/dL for men and <50 mg/dL for women or treatment of dyslipidemia; systolic blood pressure 130 mmHg, diastolic blood pressure 85 mmHg or anti-hypertensive treatment; and fasting plasma glucose 100 mg/dL or treatment of type 2 diabetes. Participants provided information regarding demographic factors, health behavior, and medical history through face-to-face interview using structured questionnaires.

We compared baseline characteristics of participants according to quercetin intake using analysis of variance for continuous variables and chi-square test for categorical variables. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) to examine the associations of quercetin intake, polymorphisms in MATE1, and their interactions, in relation to the prevalence of MetS using multivariate logistic regression models. We adjusted for age (years, continuous), sex, body mass index (BMI; kg/m^2, continuous), educational level (0, 6, >6 years), history of heart disease (no, yes), pack-years of smoking (0, <30, 30 pack years), total energy intake (kcal/d, continuous), marital status (married, not married), ethanol intake (none, 0.1-20, >20 g/d), red meat intake (g/d, continuous), dairy food intake (g/d, continuous), and vegetable and fruit intake (g/d, continuous). When we additionally adjusted for regular exercise, the results did not appreciably change, and therefore, we did not include regular exercise in the final model. We examined the associations of six SNPs in the age-and sex-adjusted logistic regression models. Interactions between quercetin intake and SNPs in MATE1, with MetS prevalence, were assessed by including a cross-product term and using a likelihood ratio test. p<0.05 was considered statistically significant. All analyses were performed using the SAS 9.3 version software (SAS Institute Inc., Cary, NC, USA).

Results and Discussion

In our study, a total of 203 MetS patients were identified (47.43%). Mean values of quercetin intake were 8.89 mg/d for men and 6.26 mg/d for women. When we compared characteristics of participants according to quercetin intake that was adjusted for energy, we found that those participants who consumed high quercetin were more likely to be male, have higher education level, regularly exercise, and consume more calories, red meat, dairy foods, and vegetables and fruits than those participants who consumed low quercetin (Table 1).

An intake of quercetin appeared to be associated with a lower prevalence of MetS; ORs (95% CIs) were 0.51 (0.27-0.94) for the 2nd quartile and 0.44 (0.24-0.84) for the 3rd quartile, compared with the 1st quartile of quercetin intake. However, we did not observe an inverse association for the top quartile of quercetin intake. Participants with only the minor allele of rs2453589 AA (adenine binds with adenine) tended to have a lower prevalence of MetS (OR=0.69, 95% CI= 0.36-1.34), compared with those participants with only the major allele GG (guanosine binds with guanosine). For rs2245639, a non-significant lower prevalence of MetS (OR=0.72, 95% CI=0.37-1.37) was observed among those participants with the AC (adenine binds with cytosine) variant, compared with those with the AA. However, other SNPs (rs2165894, rs4925026, rs2440161, rs8074784) were not significantly associated with the prevalence of MetS (Table 2). When we examined the interactions between quercetin intake and six SNPs in MATE1 in relation to the prevalence of MetS, participants who consumed moderate quercetin (2^{nd} and 3^{rd} quartiles) tended to be, in general, associated with a lower prevalence of MetS in both wild and variant alleles. For rs2453589, compared to GG genotype, OR (95% CI) for combined category of quartiles 2 and 3 was 0.39 (0.19-0.80). However, we did not find any significant interactions (*p* for interaction ≥0.37) (Table 3).

In conclusion, in this cross-sectional study of Korean adults, we found that quercetin intake was associated with a lower prevalence of MetS. Although we did not find a linear trend for the association between quercetin intake and the prevalence of MetS, participants who consumed quercetin (approximately the amount contained in 25 gram of onion) from foods had a lower prevalence of MetS compared to those who consumed low levels of quercetin. When we examined the association by genetic variant of MATE1, this

Table 1. Characteristics of participants according to energy-adjusted quercetin intake

	Quercetin intake*				*p* value**
	Q1	Q2	Q3	Q4	
Quercetin intake (mg/d)	2.2±0.7	4.1±0.6	6.2±0.9	17.1±11.4	<0.0001
Age (years)	67.4±7.8	68.4±7.6	66.6±9.3	67.2±8.2	0.46
BMI (kg/m^2)	25.5±3.3	24.8±3.4	25.0±3.2	25.0±3.1	0.40
Sex (%)					
Men	32.7	43.0	40.2	57.9	0.002
Women	67.3	57.0	59.8	42.1	
Marital status (%)					
Married	68.2	68.2	62.6	77.6	0.12
Not married	31.8	31.8	37.4	22.4	
Educational level (%)					
None	27.1	26.2	26.2	18.7	<0.001
1-6 years	50.5	46.7	43.9	29.0	
>6 years	22.4	27.1	29.9	52.3	
Pack years (%)					
None	66.4	61.7	64.5	57.0	0.85
1-30 packs/yr	16.8	18.7	19.6	22.4	
>30 packs/yr	16.8	19.6	15.9	20.6	
Ethanol intake (%)					
None	60.8	69.2	62.6	61.7	0.87
0.1-20 g/d	19.6	16.8	20.6	18.7	
>20 g/d	19.6	14.0	16.8	19.6	
Regular exercise (%)					
Yes	14.0	11.2	11.2	29.0	<0.001
No	86.0	88.8	88.8	71.0	
Total energy intake (kcal/d)	1704.8±474.8	1543.5±440.4	1572.3±411.2	1689.5±597.4	0.03
Red meat intake (g/d)	11.6±14.7	14.9±17.5	28.1±29.6	39.8±40.3	<0.001
Dairy food intake (g/d)	89.0±132.9	56.0±89.2	65.8±105.3	92.4±123.1	0.05
Vegetable and fruit intake (g/d)	332.5±208.3	391.2±223.5	400.5±308.5	444.7±243.7	0.01

Mean values of quercetin intake were 8.89 mg/d for men and 6.26 mg/d for women.

*Mean±standard deviation (SD) for continuous variables.

**Analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables.

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) for metabolic syndrome according to quercetin intake and *MATE1* polymorphisms

	Quercetin intake			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
No. of cases/non cases	60/47	46/61	41/66	56/51
Model 1 OR (95% CI)[a)]	1.00	0.57 (0.33-0.99)	0.49 (0.28-0.85)	0.86 (0.50-1.50)
Model 2 OR (95% CI)[b)]	1.00	0.49 (0.28-0.88)	0.46 (0.25-0.83)	0.86 (0.46-1.61)
Model 3 OR (95% CI)[c)]	1.00	0.51 (0.27-0.94)	0.44 (0.24-0.84)	0.83 (0.42-1.61)
	MATE1 SNPs			
rs2453589	GG	GA	AA	
No. of cases/non cases	113/105	72/95	18/25	
OR (95% CI)[a)]	1.00	0.71 (0.47-1.07)	0.69 (0.36-1.34)	
rs2165894	AA	AG	GG	
No. of cases/non cases	86/95	91/104	26/26	
OR (95% CI)[a)]	1.00	0.99 (0.66-1.48)	1.05 (0.57-1.96)	
rs4925026	TT	TC	CC	
No. of cases/non cases	68/70	97/113	38/42	
OR (95% CI)[a)]	1.00	0.91 (0.59-1.40)	0.93 (0.53-1.61)	
rs2440161	AA	AG	GG	
No. of cases/non cases	101/100	80/105	22/20	
OR (95% CI)[a)]	1.00	0.78 (0.52-1.17)	1.07 (0.55-2.09)	
rs2245639	AA	AC		
No. of cases/non cases	186/200	17/25		
OR (95% CI)[a)]	1.00	0.72 (0.37-1.37)		
rs8074784	TT	TA/AA		
No. of cases/non cases	160/179	43/46		
OR (95% CI)[a)]	1.00	1.03 (0.64-1.65)		

Abbreviations of nucleobase: A, adenine; G, guanine; T, thymine; and C, cytosin

[a)]Model 1 is adjusted for age and sex; P for trend=0.76

[b)]Model 2 is adjusted for model 1 variables and educational level (categorical; 0, ≤6, >6 years), history of heart disease (no, yes), pack-years of smoking (categorical; 0, <30, ≥30 pack years), total energy intake (continuous, kcal/d), marital status (categorical; married, not married), ethanol intake (categorical, none, 0.1-20, >20 g/d), red meat intake (continuous, g/d), and dairy food intake (continuous, g/d); P for trend=0.52

[c)]Model 3 is adjusted for variables listed in model 2 and body mass index (BMI; continuous kg/m^2); P for trend=0.67

association was more pronounced among GA/AA genotype of rs2453589 compared to GG genotype. However, non-significant interaction warrants further studies with a large sample size.

Our study is in agreement with previous studies (19-23). The European Prospective Investigation into Cancer and Nutrition (EPIC) study found that dietary intake of individual flavanols and flavonols was associated with a lower incidence of type 2 diabetes (23). A meta-analysis of prospective cohort studies showed inverse associations between flavonoid intake and risks of cardiovascular disease (22) and type 2 diabetes (20). A cross-sectional study of US women found that flavonol intake was associated with lower levels of soluble intercellular adhesion molecule-1, and soluble vascular adhesion molecule-1, a mediator of endothelial dysfunction (19). Several intervention studies have also suggested improved metabolic markers by quercetin supplementation. A randomized, placebo-controlled, crossover trial in twelve healthy men showed that oral administration of 200 mg quercetin increased S-nitrosothiol and decreased endothelin-1 concentrations, indicating endothelial function improvement (21). In a randomized, double-blind, placebo-controlled intervention trial of overweight or obese participants, systolic blood pressure and plasma oxidized low-density lipoprotein concentration were reduced following six weeks of quercetin supplementation (150 mg/d) (24).

Antioxidant activity is the major potential mechanism that flavonoids ameliorate metabolic disease progression. Flavonoids react with the reactive compounds of free radicals and stabilize the reactive oxygen species by donating hydrogen atom to free radicals (25). Flavonoids act as free-radical scavengers by preventing reaction of free radicals with nitric oxide and thus inhibiting generation of oxidized LDLs, a critical risk factor for atherosclerosis (26). Flavonoids activated anti-inflammatory activity *in vitro* or in cellular models by inhibiting formation and activities of different pro-inflammatory mediators such as eicosanoids, cytokines, adhesion molecules and C-reactive protein (27).

The strengths of our study include its being the first Korean population-based epidemiologic study of quercetin and MetS, its

Table 3. Interactions between quercetin intake and *MATE1* polymorphisms in relation to the prevalence of metabolic syndrome

SNP rs number	Quercetin intake			*p* for heterogeneity
	Quartile 1	Quartiles 2 and 3	Quartile 4	
rs2453589				
GG	1.00	0.55 (0.26-1.14)	0.89 (0.38-2.07)	0.78
GA/AA	0.90 (0.38-2.13)	0.39 (0.19-0.80)	0.67 (0.27-1.68)	
rs2165894				
AA	1.00	0.18 (0.08-0.43)	0.67 (0.24-1.85)	0.59
AG/GG	0.40 (0.17-0.98)	0.37 (0.16-0.82)	0.39 (0.15-0.98)	
rs4925026				
TT	1.00	0.36 (0.15-0.89)	0.56 (0.18-1.78)	0.37
TC/CC	0.64 (0.26-1.56)	0.35 (0.15-0.81)	0.64 (0.26-1.60)	
rs2440161				
AA	1.00	0.38 (0.17-0.83)	0.82 (0.31-2.14)	0.91
AG/GG	0.56 (0.23-1.32)	0.32 (0.15-0.70)	0.49 (0.20-1.20)	
rs2245639				
AA	1.00	0.51 (0.29-0.90)	0.83 (0.41-1.66)	0.98
AC/CC	1.60 (0.31-8.25)	0.34 (0.11-1.06)	1.13 (0.31-4.22)	
rs8074784				
TT	1.00	0.49 (0.27-0.90)	0.73 (0.35-1.52)	0.48
TA/AA	1.17 (0.37-3.77)	0.47 (0.20-1.13)	1.38 (0.49-3.87)	

Abbreviations of nucleobase: A, adenine; G, guanine; T, thymine; and C, cytosin

*Adjusted for age, sex, body mass index (BMI; continuous kg/m^2), educational level (categorical; 0, ≤6, >6 years), history of heart disease (no, yes), pack-years of smoking (categorical; 0, <30, ≥30 pack years), total energy intake (continuous, kcal/d), marital status (categorical; married, not married), ethanol intake (categorical, none, 0.1-20, >20 g/d), red meat intake (continuous, g/d), and dairy food intake (continuous, g/d)

examination of gene and diet interactions, its case ascertainment by direct measurement of biomarkers, and adjustment for potential confounding factors. Our study has limitations. Quercetin database was not thoroughly established and therefore we cannot rule out the possibility of misclassification. However, misclassification may not differ by case status. Also, a cross-sectional design of our study may not allow us to exclude the possibility of the reverse causation. Relatively small sample size could limit our ability to detect a small effect. Larger studies are needed to replicate major findings of our study.

In conclusion, quercetin intake may be inversely associated with MetS prevalence in a Korean population. Our previous novel finding that MATE1 is a transporter of quercetin in the liver and intestine of human (28) suggest the need of large prospective studies of interaction between flavonoids and variants in the MATE1 gene in relation to metabolic disorder diseases.

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Disclosure The authors declare no conflict of interest.

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