

Original Article

Association of GCKR rs780094 polymorphism with circulating lipid levels in type 2 diabetes and hyperuricemia in Uyghur Chinese

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Abstract: To investigate the relationship between a GCKR rs780094 polymorphism and lipid profiles in the Xinjiang Uyghur population in China. 980 type 2 diabetes mellitus (T2DM) patients, 1017 hyperuricemia (HUA) and 1185 healthy controls were included in this study. After genotyping of rs780094 by Sequenom Mass ARRAY system, chi-square test and logistic regression analysis were used for association analysis as well as a genotype-phenotype analysis. We found that the serum concentration of TC ($P<0.001$) was significantly higher and HDL-C ($P<0.001$) was lower in T2DM than in control participants. Subjects with HUA had a significantly higher TG ($P=0.003$) and lower HDL-C ($P<0.001$) than control participants. Additionally, under the recessive model, rs780094 was shown to be associated with the risk of HUA ($P=0.015$, OR=1.311), particularly in males ($P=0.047$, OR=1.330). Subsequent interaction analysis between rs780094 and lipid parameters showed that the TG level was positively correlated with HUA in the rs780094- AA+AG carriers ($P=0.005$). The TC concentrations showed to be associated with T2DM in the rs780094- AA+AG carriers ($P<0.001$). The association between lipid parameters and gender showed that significantly higher TG levels ($P<0.001$) and lower HDL-C levels ($P<0.001$) were observed in female HUA. Higher LDL-C levels were found in male HUA ($P=0.015$). Moreover, statistically higher TC levels and lower HDL-C levels were found both in male and female T2DM cases (TC: male: $P<0.001$, female: $P=0.014$. HDL-C: male: $P<0.001$, female: $P<0.001$). To conclude, our results demonstrated that different genotypes of rs780094 had different effects on blood lipids in HUA and T2DM patients in a Uyghur population. Gender was also one of the factors influencing blood lipid levels.

Keywords: GCKR, type 2 diabetes, hyperuricemia, dyslipidemias

Introduction

Exome-wide association study of plasma lipids in Diabetes mellitus (DM) and hyperuricemia (HUA) are both metabolic syndromes characterized by insulin resistance, dyslipidemia, hyperglycemia, hypertension and abdominal obesity [1]. The prevalence of DM and HUA are increasing rapidly in developing countries due to economic development, lifestyle changes, and an increasingly aging population. These diseases also contribute to a considerably increased all-cause mortality, cardiovascular risk, and atherosclerotic burden. They not only have a seri-

ous impact on the quality of life, but have also developed into huge social and economic burdens. Both DM and HUA are multifactorial diseases. In addition to environmental risk factors, such as poor nutrition habits, lack of exercise and cigarette smoking, genetic risk factors also contribute to DM and HUA. As such, genome-wide association studies (GWAS) have discovered susceptibility loci associated with DM and HUA [2, 3]. Genetic loci associated with serum levels of biomarkers associated with metabolic traits such as high levels of low density lipoprotein (LDL) have also been identified [4, 5]. However, studies showed that dyslipidemia

Table 1. Characteristics of study participants

Characteristics	Control (1185)	T2DM (980)	HUA (1017)	P	P (C/T2DM)	P (C/HUA)	P (T2DM/HUA)
Age (years)	47.08±11.65	51.16±9.70	46.83±12.15	<0.001*	<0.001*	0.942	<0.001*
Males/females	764/421	614/366	628/389	0.400	-	-	-
BMI (kg/m ²)	27.23±2.65	27.59±3.67	27.68±4.85	0.005*	0.030*	0.027*	0.961
FBG (mmol/L)	4.93±0.54	9.52±3.26	4.98±0.67	<0.001*	<0.001*	0.142	<0.001*
UA (mmol/L)	281.76±68.82	271.17±70.19	473.34±93.28	<0.001*	0.001*	<0.001*	<0.001*
TG (mmol/L)	2.32±2.00	2.42±1.98	2.58±1.66	0.004*	0.588	0.003*	0.149
TC (mmol/L)	4.22±1.70	4.65±1.53	4.26±1.64	<0.001*	<0.001*	0.916	<0.001*
HDL-C (mmol/L)	1.23±0.31	0.97±0.31	1.00±0.34	<0.001*	<0.001*	<0.001*	0.348
LDL-C (mmol/L)	2.78±0.61	2.85±0.82	2.84±0.60	0.022*	0.055	0.070	0.949

Continuous variables are expressed as mean ± standard deviation. The *P*-value of continuous variables was calculated by one-way ANOVA among three groups. The *P*-value of the two-two comparisons was calculated by a post-hoc multiple comparisons test. **P*<0.05.

Table 2. Genotype and allele distributions of rs780094 among the study participants

Gender Groups (n)		Genotype				Allele			Recessive model	
		GG (%)	AG (%)	AA (%)	P	G (%)	A (%)	P	OR (95% CI) ^d	P ^d
All	T2DM (980)	340 (34.69)	461 (47.04)	179 (18.27)	0.099 ^a	1141 (58.21)	819 (41.79)	0.089 ^a	1.154 (0.918-1.451) ^a	0.219
	HUA (1017)	324 (31.86)	490 (48.18)	203 (19.96)	0.001 ^{b,*}	1138 (55.95)	896 (44.05)	0.001 ^{b,*}	1.311 (1.053-1.633) ^b	0.015*
	Control (1185)	444 (37.47)	552 (46.58)	189 (15.59)	0.150 ^c	1440 (60.76)	930 (39.24)	0.148 ^c	1.124 (0.895-1.411) ^c	0.314
Male	T2DM (614)	224 (36.48)	282 (45.93)	108 (17.59)	0.087 ^a	730 (59.45)	498 (40.55)	0.082 ^a	1.184 (0.884-1.586) ^a	0.258
	HUA (628)	200 (31.85)	307 (48.89)	121 (19.27)	0.001 ^{b,*}	707 (56.29)	549 (43.71)	0.001 ^{b,*}	1.330 (1.004-1.762) ^b	0.047*
	Control (764)	311 (40.71)	336 (43.98)	117 (15.31)	0.105 ^c	958 (62.70)	570 (37.30)	0.111 ^c	1.087 (0.810-1.460) ^c	0.579
Female	T2DM (366)	116 (31.69)	179 (48.91)	71 (19.40)	0.694 ^a	411 (56.15)	321 (43.85)	0.661 ^a	1.115 (0.771-1.612) ^a	0.563
	HUA (389)	124 (31.88)	183 (47.04)	82 (21.08)	0.505 ^b	431 (55.40)	347 (44.60)	0.454 ^b	1.289 (0.906-1.833) ^b	0.158
	Control (421)	133 (31.59)	216 (51.31)	72 (17.10)	0.796 ^c	482 (57.24)	360 (42.76)	0.770 ^c	1.149 (0.802-1.647) ^c	0.449

OR, odds ratio; 95% CI, 95% confidence interval. The frequency of genotypes and alleles are presented as a percentage. The distributions of genotypes are all within HWE. The *P* value of categorical variable was calculated by the chi-square test. The *P* value of the association of rs780094 was calculated by the logistic regression analysis.

*T2DM compared with controls. ^bHUA compared with controls. ^cHUA compared with T2DM. ^dAdjusted for sex, age and BMI. **P*<0.05.

were associated with the development of atherosclerosis and cardiovascular disease [6, 7]. In order to investigate metabolic risk factors such as dyslipidemia, it is of particular interest to cluster genetic loci that have been linked to metabolic traits.

Glucokinase (GCK), expressed in the liver and in pancreatic beta cells, encodes the key enzyme for the first rate-limiting step of glycolysis, regulating glucose balance and glucose-stimulated insulin secretion [8]. GCK activity is controlled by the glucokinase regulatory protein (GCRP), which binds to GCK. Its inhibitory effect is enhanced by fructose 6-phosphate and antagonized by fructose 1-phosphate. The glucokinase regulator gene (*GCKR*) encodes GCRP. The most commonly reported SNP in *GCKR*, rs780094, has been shown by GWAS studies to be associated with insulin levels [9], fasting glucose [9, 10], triglycerides (TG) [11], uric acid [12] and susceptibility to type 2 DM (T2DM) [13-15] and HUA [16]. In the European population associations between rs780094

A-allele and either lower fasting blood glucose (FPG) levels, less insulin resistance, higher fasting serum TG levels or a lower risk of T2DM have been confirmed [9, 17]. A meta-analysis proved that rs780094 had an association with the opposite effects on fasting TG levels and FPG by analyzing Caucasians, African Americans, Hispanics, Asian Indians, Chinese and Malays and with a decreased risk of T2DM in European populations [18]. In a Japanese study, a significant association of the A allele of *GCKR* rs780094 with increased fasting TG levels, decreased FPG and a reduced risk of T2DM were reported [13]. A significant association of rs780094 with uric acid and triglycerides concentrations was confirmed in a European [19] and Han Chinese male [20] study. It is of interest to study metabolic risk factors in populations with high prevalence of T2DM and metabolic syndrome. However, the association between rs780094 and lipid traits remained unclear among individuals with T2DM or HUA.

The Uygur population, accounting for 46% of the population of the Xinjiang Uygur Autonomous

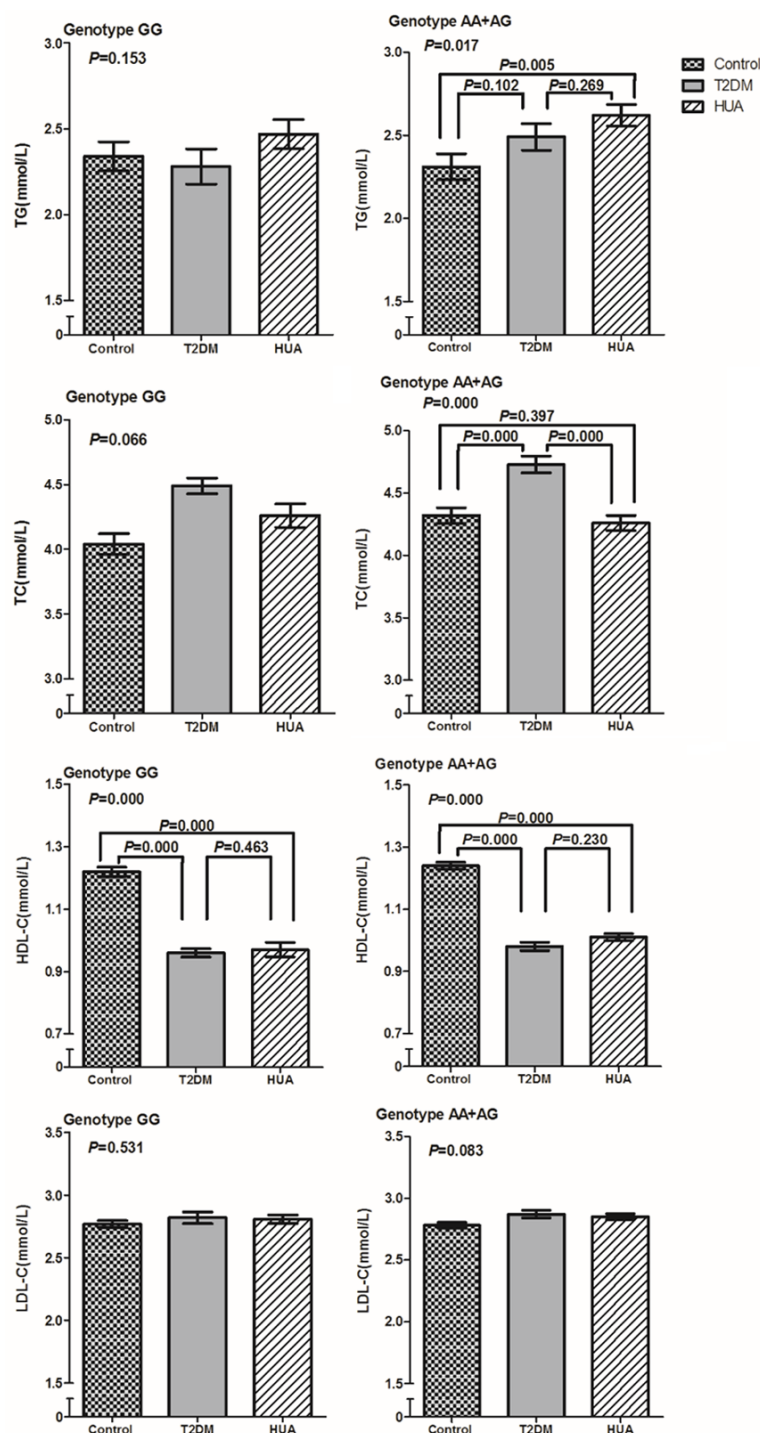


Figure 1. The comparison of lipid parameters among participants with different genotypes of rs780094. *P* values were adjusted by age, sex and BMI.

Region of China, originates from a two-way admixture between Caucasians (42.6%) and Asians (57.4%) [21]. Because migration is rare, the Uyghur are an ideal population in which to discover genetic factors for multifactorial diseases such as T2DM and HUA. This study was con-

ducted to investigate the association between the GCKR polymorphism rs780094 with lipid profile in T2DM cases, HUA cases and healthy controls from the Uyghur region of China.

Materials and methods

Study subjects

All 3182 subjects, aged 18-76 years old, were recruited for this study from the Xinjiang Uyghur Autonomous Region of China. Among them, 980 subjects were diagnosed with T2DM without HUA and 1017 subjects were diagnosed with HUA without T2DM at the First Affiliated Hospital of Xinjiang Medical University between January 2012 and December 2013. T2DM was defined using the American Diabetes Association 2009 criteria [22] (fasting plasma glucose ≥ 7.0 mmol/L (≥ 126 mg/dL)) or as self-reported current diabetes treatments via a survey. HUA was defined as serum uric acid (SUA) ≥ 416 mmol/L (7 mg/dl, males) or SUA ≥ 357 mmol/L (6 mg/dl, females), which are widely accepted diagnostic criteria [23].

The 1185 healthy controls were randomly selected from participants in a health examination by the First Affiliated Hospital of Xinjiang Medical University. Control participants had no personal or familial history of T2DM, HUA or any other serious illness. Participants with known systemic diseases, including DM, hypertension, cardiovascular disease, renal or liver disease, gastrointestinal disease, pulmonary disease or cancer were excluded.

Participants were interviewed using a structured questionnaire by trained personnel to col-

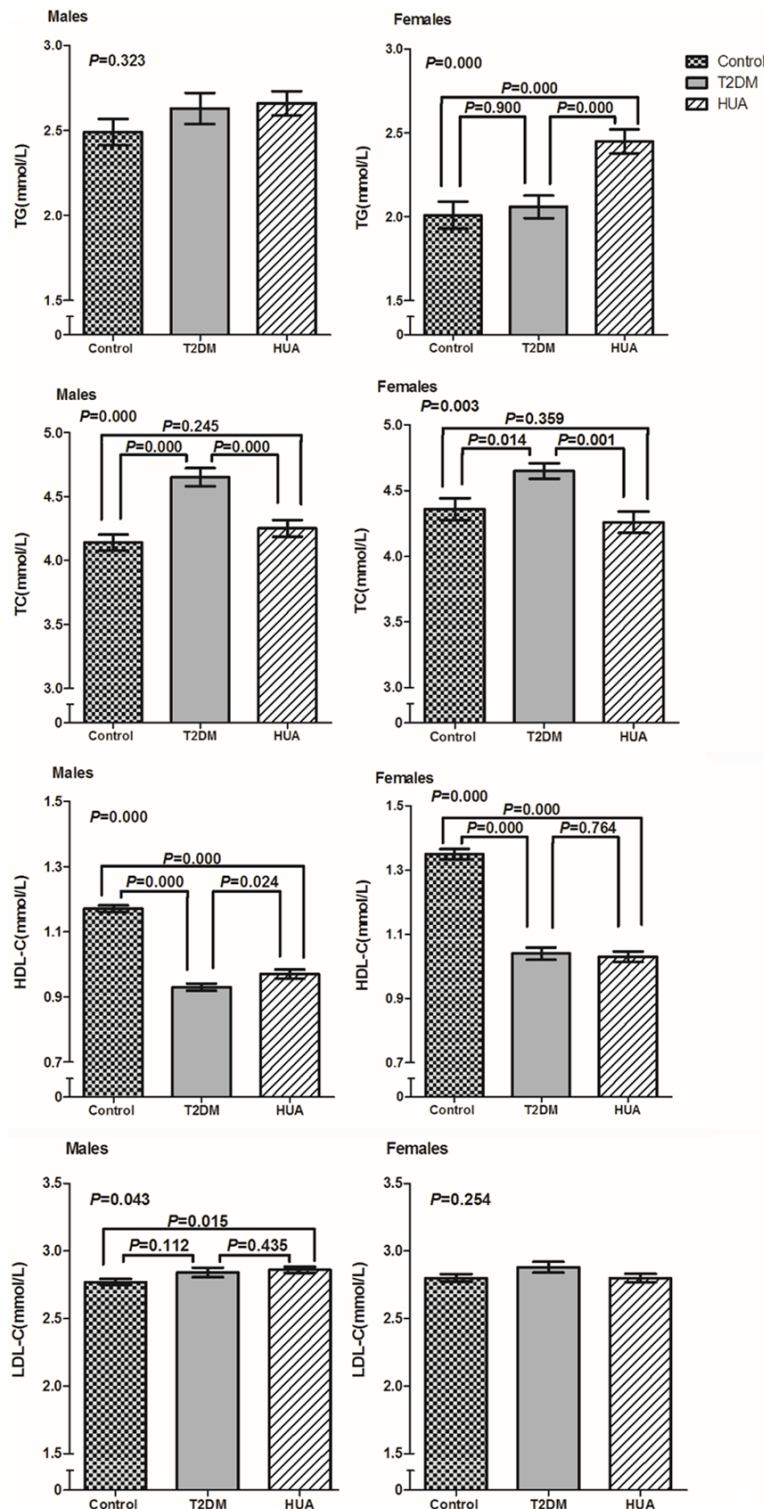


Figure 2. The comparison of lipid parameters among participants according to gender. *P* values were adjusted by age and BMI.

lect demographic characteristics (age, gender, etc.). Body weight and height were measured with subjects wearing light indoor clothing and

barefoot. Body mass index was calculated as the subject's weight (kg) divided by the square of the subject's height (m²). Waist circumference was measured midway between the lower rib and iliac crest. For clinical chemistry assays, serum was separated from peripheral venous blood samples obtained from each participant after a 12-hour fast and stored at -70°C. Blood was drawn from the antecubital vein of the arm. The blood samples were drawn for biochemical measurements including FBG, UA, total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) in accordance with the procedures recommended by the Clinical Laboratory Department of the First Affiliated Hospital of Xinjiang Medical University. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University.

Single-nucleotide polymorphism genotyping

Genomic DNA was isolated from peripheral blood leukocytes using the Wizard Genomic DNA Purification kit (Promega Corp, Madison, WI, USA) according to the manufacturer's protocol. The SNP was genotyped using the Sequenom MassARRAY system (San Diego, CA, USA) according to the iPLEX Gold Application Guide. The sequences of the primers of GCKR rs780094 were as follows: F-ACGTTGGATGAGGGCCCCA-GTTTTTAC, R-ACGTTGGAT-GCCCGCCTCAACAAATGTAT. The SNP passed quality control criteria with a genotyping call rates > 90%.

Statistical analyses

In this study, statistical analyses were performed with the Statistical Package for Social Sciences version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean \pm standard deviation and were analyzed by one-way ANOVA. The chi-square test was used in the comparison of the rate of genotype and allele distributions among the study participants. For all cases and controls, the Hardy-Weinberg equilibrium (HWE) of the genotype distribution was tested using the homogeneity χ^2 test. Logistic regression analysis was carried out to study the effect of the odds ratio (OR) and 95% confidence intervals (95% CIs). *P*-values of <0.05 were considered statistically significant.

Results

Characteristics of the study population

Table 1 shows the baseline characteristics of the T2DM, HUA and control subjects in the Uygur population. There were differences in the serum concentration of TG ($P=0.004$), TC ($P<0.001$), HDL-C ($P<0.001$) and LDL-C ($P=0.022$) among the T2DM, HUA and control groups. Subjects with T2DM had a significantly higher TC ($P<0.001$) and lower HDL-C ($P<0.001$) than control participants. Subjects with HUA had a significantly higher TG ($P=0.003$) and lower HDL-C ($P<0.001$) than control participants. The serum concentration of TC in T2DM patients was higher ($P<0.001$) compared with HUA patients.

Distribution of rs780094 among HUA, T2DM patients and controls

Table 2 shows the distribution of genotypes and alleles of GCKR rs780094. This SNP conformed to HWE in all groups (data not shown). The frequencies of the GG, AG and AA genotypes were 37.47%, 46.58% and 15.59% respectively, among the controls. Meanwhile, they were 34.69%, 47.04% and 18.27% respectively, in the T2DM group, and 31.86%, 48.18% and 19.96 % respectively, in the HUA group. The distribution of rs780094 genotypes and alleles showed a statistical difference only between the HUA patients and control participants ($P=0.001$ and $P=0.001$ respectively). A further analysis by gender were observed a sig-

nificant difference between patients with HUA and control participants ($P=0.001$ and $P=0.001$ respectively) in male genotypes and alleles only.

After adjusting for sex and age, rs780094 was found to be associated with HUA under a recessive model ($P=0.015$, OR=1.311, 95% CI=1.053-1.633). Additionally, significant difference was found in male groups under the recessive model ($P=0.047$, OR=1.330, 95% CI=1.004-1.762) between HUA group and controls.

Figure 1 shows a comparison of the lipid parameters among participants with different rs780094 genotypes. The level of TG was associated with the risk of HUA in genotype AA+AG ($P=0.005$) compared to the control group. The TC concentrations showed statistical differences with genotype AA+AG between T2DM cases ($P<0.001$) and the control group, and between HUA cases ($P=0.000$) and T2DM cases. The level of HDL-C showed statistical associations between T2DM and the control group with genotype GG ($P<0.001$) and AA+AG ($P<0.001$). Additionally, the significant differences were also found between HUA and the control group with genotype GG ($P<0.001$) and AA+AG ($P<0.001$).

Association of lipid parameters with HUA and T2DM in different gender groups

Figure 2 shows the association of lipid parameters with metabolic syndromes in different gender groups. The TG levels in HUA cases were significantly higher than controls ($P<0.001$) and T2DM cases ($P<0.001$) in the female group. Moreover, the TC levels in T2DM cases were statistically higher than controls ($P<0.001$) and HUA cases ($P<0.001$) in males. A higher level of TC was also found in females with T2DM cases compared to controls ($P=0.014$) and HUA cases ($P=0.001$). However, the level of HDL-C was lower in HUA ($P<0.001$, $P<0.001$) and T2DM cases ($P<0.001$, $P<0.001$) compared to controls in both males and females. Additionally, the LDL-C levels was higher in HUA cases ($P=0.015$) compared to controls in males.

Discussion

It has been suggested that circulating lipid concentrations in the blood are independent risk

factors for various tumors [24] and vascular diseases [25]. In addition it is well established that T2DM and HUA are more likely to be dyslipidemia than the general population. The coexistence of lipid abnormalities and T2DM or HUA can further increase the risk of cardiovascular disease. Dyslipidemia in patients with T2DM were characterized as high TG, low LDL-C [26], TC as well as HDL-C concentration [27]. A recent study revealed that TG was the best lipid index related to HUA [28]. However there are conflicting data about the role of single lipid species in HUA. The relationship between lipids and T2DM or HUA varied in different populations. In this study, we observed that the concentrations of TC were significantly associated with T2DM. Following TC, the lower HDL-C levels were associated with T2DM. Additionally, HUA patients were characterized as higher serum concentrations of TG and lower HDL-C in our study.

The GCKR rs780094 has been shown to be associated with several circulating lipid concentrations in various diseases among different ethnic populations. The association between the A allele of rs780094 and higher levels of TG were reported in Europeans [17], Han Chinese populations [29], the Japanese population [13] and the Sri Lankan population [30]. Hadarits *et al* [31] stratified metabolic syndrome patients into four quartile groups according to the available TG values. They found that the frequency of the homozygote minor allele (AA) of rs780094 was higher in q4 (q4 represented TG > 2.83 mmol/L), but allele frequencies showed no further significant differences in different groups. Additionally, the minor A-allele of rs780094 was shown to be associated with an increased level of TG, a minor elevation of total fasting serum TC, World Health Organization-defined dyslipidemia and a modestly decreased risk of T2DM in Danes [9]. Mohas *et al* [11] also found that the minor allele (A) of rs780094 was associated with elevated serum TG levels in Hungarian subjects with T2DM and metabolic syndrome. Hishida *et al* [32] showed that haplotypes containing the G allele of rs780094 were significantly associated with a reduced risk of dyslipidemia (TG \geq 150 mg/dL and/or HDL-C <40 mg/dL) with an OR of 0.88 (95% CI=0.81-0.95) in the Japan Multi-Institutional Collaborative Cohort Study, but TG and HDL-C levels were not significantly associated with rs780094. Lee *et al* [33] showed that major allele

(AA) carriers of rs780094 had significantly higher TC and TG levels in Korean adults and higher TC and LDL-C levels in Korean children after adjustment for age, sex, and body mass index. Qi, *et al* [29] showed that the rs780094-A allele was highly associated with higher levels of TC and increased risk of dyslipidemia under either an additive or dominant model in Han Chinese individuals. These studies demonstrate that both the frequency and function of this SNP differs among different populations. Our results suggested that the recessive model of rs780094 polymorphism appeared to show an increased risk of HUA in Uyghur male population. Additionally, HUA patients with rs780094-AA+AG were associated with higher concentrations of the TG levels. And T2DM patients with rs780094-AA+AG were associated with higher concentrations of the TC levels. Our results showed that GCKR not only affects blood glucose and uric acid levels, but is also associated with lipid levels. To the best of our knowledge, this is the first study aiming to investigate the association between rs780094 and lipid profile among T2DM cases, HUA cases and healthy controls in the Uyghur population of China.

The importance of sexual dimorphisms including both sexes in clinical trials and basic research has been emphasized recently. Understanding how and why metabolic processes differ by sex will enable clinicians to target and individualized therapies based on gender. In addition to sex hormone, the particular genetic variants in metabolism-related genes also have an effect on sex-specific metabolism [34]. A previous study has found that men have significantly higher TG, LDL-C, and lower HDL-C compared to women in Beijing, China [35]. Another study has found that males have lower levels of TC, LDL-C, and HDL-C than females in Ethiopian-American adults [36]. In this study, we observed that TG levels were significantly higher in HUA females cases, LDL-C levels was higher in HUA male cases. However, TC levels were significantly higher in T2DM cases both in males and females. HDL-C levels were lower in HUA and T2DM cases both in males and females.

Several strengths and limitations of our case-control study should be mentioned. Firstly, because the Uyghur population is admixed, but homogeneous, this minimizes the risk of envi-

ronmental confounders and increases the ability to discover genetic effects. Secondly, the sample size was relatively small and might not be sufficient to discover an association for a variant with only moderate or minor effects on lipid concentrations. Thirdly, we only assessed one SNP for its relationship with T2DM and HUA. Other genetic polymorphisms in *GCKR* might play an important role. Therefore, further studies utilizing a larger sample size with other common and rare alleles are required.

In conclusion, this case-control study shows that rs780094 displays an association with HUA risk in Uyghur Chinese males. The genotype of rs780094-AA+AG showed significant interaction with the concentrations of TG levels in HUA patients. The TC levels were higher for the rs780094-AA+AG genotypes than for carriers of the GG genotypes in T2DM patients. It showed that the TG and LDL-C levels were affected by HUA in Uyghur population.

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Disclosure of conflict of interest

None.

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