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ORIGINAL ARTICLE

Plasma tyrosine and its interaction with low high-density lipoprotein cholesterol and the risk of type 2 diabetes mellitus in Chinese

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ABSTRACT

Aims/Introduction: Metabolomic markers have the potential to improve the predicting accuracy of existing risk scores for type 2 diabetes mellitus. The present study aimed to test the associations between plasma tyrosine and type 2 diabetes mellitus with special attention to identifying possible cut-off points for type 2 diabetes mellitus, and its interactive effects with low high-density lipoprotein cholesterol (HDL-C) and/or high triglyceride for type 2 diabetes mellitus.

Methods: From 27 May 2015 to 3 August 2016, we retrieved the medical notes of 1,898 inpatients with type 2 diabetes mellitus as the cases, and 1,522 individuals without diabetes as the controls who attended annual medical checkups from the same tertiary care center in Jinzhou, China. Logistic regression analyses were carried out to obtain odds ratios (ORs) and 95% confidence intervals (CIs). Restricted cubic spline analysis nested in the logistic regression analysis was used to identify possible cut-off points of tyrosine for type 2 diabetes mellitus. The additive interaction was used to estimate interactions between high tyrosine and low HDL-C in type 2 diabetes mellitus patients.

Results: The OR of tyrosine for type 2 diabetes mellitus did not increase until 46 μmol/L and after that point, the OR rapidly rose with increasing tyrosine in a nearly linear manner. If 46 μmol/L was used to define high tyrosine, high tyrosine was associated with an increased OR of type 2 diabetes mellitus (adjusted OR 1.88, 95% CI 1.44–2.45). The presence of low HDL-C greatly enhanced the ORs of tyrosine for type 2 diabetes mellitus from 1.11 (95% CI 0.82–1.51) to 54.11 (95% CI 33.96–86.22) with significant additive interaction.

Conclusions: In Chinese adults, tyrosine >46 μmol/L was associated with increased odds of type 2 diabetes mellitus, which was contingent on low HDL-C.

INTRODUCTION

Type 2 diabetes mellitus has become a heavy burden on limited medical resources. In China, the prevalence of diabetes reached 11.6% in 2010, affecting approximately 113.9 million adults[1]. Type 2 diabetes mellitus stems from interactions between genetic predispositions and environmental factors. Among the environmental factors, overweight and obesity are believed to play a causal role in the increasing burden of type 2 diabetes mellitus[2]. Obesity, especially central obesity, often appears in clusters with insulin resistance, high triglyceride and low high-density lipoprotein cholesterol (HDL-C); that is, so-called metabolic syndrome[3]. Although type 2 diabetes mellitus is

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preventable by lifestyle modifications[4], it remains a challenge to accurately predict diabetes at individual levels[5].

Previous animal experiments found that insulin resistance was connected with metabolism of tyrosine[6,7], and elevated tyrosine levels might inhibit the insulin signaling pathway[7], which is related to the development of type 2 diabetes mellitus. In addition, it is believed that there is an association between hyperglycemia and tyrosine nitration[8], suggesting that altered levels of tyrosine might reflect the degree of oxidative stress or inflammation in people with diabetes or prediabetes conditions. Consistently, human studies also observed that increased plasma concentration of tyrosine is associated with hyperglycemia[9], and might be one of the manifestations of subclinical inflammation and immune activation[10]. The relationship between tyrosine levels and the risk of type 2 diabetes mellitus was robust by ethnicity and study designs[11–14]. It is interesting to note that although plasma levels of many amino acids have been repeatedly linked to type 2 diabetes mellitus, tyrosine has the strongest association with the occurrence of type 2 diabetes mellitus, independent of obesity[13]. To our knowledge, only a few studies carried out in Chinese populations tested the association between tyrosine and type 2 diabetes mellitus.

Both high triglyceride and low HDL-C are components of metabolic syndrome and markers of insulin resistance[3], but triglyceride and HDL-C might link to insulin resistance through different mechanisms or pathways. In this regard, HDL-C might upregulate phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) and acetyl-CoA carboxylase to increase glucose uptake in the muscle and insulin sensitivity[15], whereas high insulin levels might increase levels of triglyceride through selectively activating key enzymes involved in the synthesis of free fatty acids[16]. It is unknown whether there are interactions of high tyrosine and low HDL-C or high triglyceride for type 2 diabetes mellitus.

In the present cross-sectional study, we aimed to test the association between plasma levels of tyrosine and type 2 diabetes mellitus. We also explored possible cut-off points of tyrosine for type 2 diabetes mellitus and if possible, further tested any additive interactions between higher tyrosine levels and lower HDL-C and/or higher triglyceride for type 2 diabetes mellitus in Chinese patients with type 2 diabetes mellitus.

METHODS

Study population and settings

Liaoning Medical University First Affiliated Hospital, located in Jinzhou, Liaoning Province, China, is a comprehensive tertiary care center serving a population of 3.1 million. In 2013, the metabolomic laboratory was established, which offered metabolomic assays to all patients including outpatients or inpatients, or those individuals at their health examinations who agreed to pay the fee. A total of 71,020 patients having a metabolomic profile were measured from 27 May 2015 to 3 August 2016, in Liaoning Medical University First Affiliated Hospital. Among them, 1,898 patients were diagnosed with type 2 diabetes mellitus, and their electronic medical records were retrieved. Patients aged <18 years, and lacking information on height, weight and blood pressure were not included. Based on these exclusion criteria, 1,032 diabetes patients diagnosed by the 1999 World Health Organization's criteria[17] or treated with antidiabetic drugs were remaining and were designated to the case group. During this period, a total of 10,648 individuals without diabetes from the hospital's catchment areas participated in a health examination, and 4,488 of them without information on height, weight and blood pressure were excluded. Of the remaining 6,160 individuals, 1,522 individuals with metabolomic profiles measured using the same method (aged >18 years) were retrieved and used as the control group. Finally, we organized a hospital-based non-matched case–control study with 2,554 individuals (1,032 cases and 1,522 controls) to address our research questions. The Ethics Committee for Clinical Research of FAHLMU approved the ethics of the study, and informed consent was waivered due to the retrospective nature of the study, which is consistent with the Declaration of Helsinki.

Data collection and definitions

The retrieved data in the cases included demographic and anthropometric information, and current clinical factors, drugs and diabetes complications. The clinical parameters included glycated hemoglobin, blood pressure, lipid profile, plasma creatinine, urinary creatinine and albumin. Diabetes complications included coronary heart disease, cerebrovascular disease, diabetic retinopathy and diabetic nephropathy. The details use of medications were documented, including oral antidiabetic drugs (OADs) and insulin, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and other antihypertensive drugs, statins, and other lipid-lowering drugs.

The retrieved data in the control group included demographic information, anthropometric information and laboratory assays. In this hospital, standardized procedures were used to measure anthropometric indices. Participants wore light clothing and no shoes. Height and bodyweight were measured to the nearest 0.5 cm and 0.1 kg, respectively. Blood pressure was measured using standard mercury sphygmomanometers and appropriate sizes of adult cuffs on the right arm, after a 10-min rest in a sitting position. Age was calculated as the period in years from the date of birth to the date of inpatient hospitalization or health examination. Body mass index (BMI) was calculated to estimate adiposity as the ratio of weight in kilograms to height squared in meters, and categorized for overweight and obesity according to Chinese adults' criteria[18]. The definition of metabolic syndrome was used to define low HDL-C and high triglyceride[19]; that is, low HDL-C defined as <1 mmol/L in men and 1.3 mmol/L in women, whereas high triglyceride was defined as >1.7 mmol/L.

Laboratory assays

LC-MS/MS analysis

Details of the metabolomics assessment method were published previously[20]. Briefly, capillary whole blood was taken after at least 8-h fasting, which was stored as dried blood spot and used in the assay of metabolomics. Metabolites in dried blood spot were measured by direct infusion mass spectrometry technology equipped with the AB Sciex 4000 QTrap system (AB Sciex, Framingham, MA, USA). High-purity water and acetonitrile from Thermo Fisher (Waltham, MA, USA) were used as the diluting agent and mobile phase. 1-Butanol and acetyl chloride from Sigma-Aldrich (St Louis, MO, USA) were used to derive samples. Isotope-labeled internal standard samples of 12 amino acids (NSK-A) were purchased from Cambridge Isotope Laboratories (Tewksbury, MA, USA), while standard samples of the amino acids were purchased from Chrom Systems (Grafelfing, Germany).

Biochemical assays

After at least 8-h of fasting, 8.5 mL of venous blood was drawn from each of the participants in the morning between 08.00 and 09.30 hours. Laboratory assays were carried out at a special diagnostic laboratory. Lipid profiles were analyzed by an automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan). The level of HDL-C and low-density lipoprotein cholesterol (LDL-C) was analyzed by the selective solubilization method (Determiner L HDL, LDL test kit; Kyowa Medex, Tokyo, Japan).

Statistical analysis

Data with normal distribution were expressed as the mean ± standard deviation (SD) or median (interquartile range). Student's *t*-test or the Mann–Whitney *U*-test were carried out to determine significant differences in the continuous data, or the χ^2-test (or Fisher's exact test where appropriate) was used to compare differences in categorical variables between the type 2 diabetes mellitus group and the healthy control group. Binary logistic regressions were carried out to obtain odds ratios (OR) and 95% confidence intervals (CI) of tyrosine for type 2 diabetes mellitus. A structured adjustment scheme was used to adjust for traditional risk factors for type 2 diabetes mellitus. First, we obtained the unadjusted OR. Second, we adjusted ORs for age, sex, BMI, systolic blood pressure, LDL-C, HDL-C and triglyceride to obtain the adjusted OR of tyrosine for type 2 diabetes mellitus.

Restricted cubic splines are piecewise cubic polynomials connected across different intervals of a continuous variable, which can fit sharply curving shapes[21]. To capture the full-range association between tyrosine and type 2 diabetes mellitus, and to identify possible cut-off points of tyrosine for type 2 diabetes mellitus, we used restricted cubic splines in logistic regression. We used this method in a number of our previous studies to identify cut-off points of lipids for cancer in type 2 diabetes mellitus[22]. Briefly, we chose four knots at quantiles 0.05, 0.35, 0.65 and 0.95, as suggested by Harrell[21]. ORs between two points of height can be estimated by EXP (the exponential functions with base e and denoted by e^x; Y2 − Y1), where Y2 and Y1 were the values of restricted cubic spline functions at tyrosine levels 2 and 1. As before, a cut-off point was selected if the odds of type 2 diabetes mellitus rapidly increased by visual checking of the curve. Further confirmation analysis was carried out by stratifying tyrosine into a categorical variable at the selected cut-off points in logistic regression analysis.

Interactions between high tyrosine and low HDL-C (and high triglyceride) were estimated using additive interaction[23]. Three measures; that is, relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP) and synergy index (S), were used to estimate additive interactions. A significant RERI >0, additive interaction >0 or S >1 indicates an additive interaction or synergistic effect between high tyrosine and low HDL-C (or high triglyceride) for type 2 diabetes mellitus. A calculator is available at http://www.epinet.se.22.

Sensitivity analysis

Use of non-incident type 2 diabetes mellitus was a potential source of bias. We carried out a sensitivity analysis with exclusion of 631 patients with duration of diabetes >2 years to check changes in the effect sizes of high tyrosine for type 2 diabetes mellitus.

All the analyses were carried out using the Statistical Analysis System (release 9.2; SAS Institute Inc., Cary, North Carolina, USA), and a two-tailed *P*-value <0.05 was considered statistically significant.

RESULTS

Characteristics of the study population

The 2,554 participants had a mean age of 50.7 years (SD 14.7 years), mean height of 168.4 cm (SD 8.2 cm), mean bodyweight of 72.3 kg (SD 13.4 kg) and mean BMI of 25.4 kg/m² (SD 3.6 kg/m²). Compared with their counterparts without diabetes, the cases had an older age, shorter height, higher systolic blood pressure and diastolic blood pressure. They were also more likely to have lower levels of HDL-C and LDL-C, but higher levels of triglyceride and tyrosine. Patients with type 2 diabetes mellitus had a median of 5 years (25th to 75th: 0–10) of duration of diabetes. Furthermore, they had a mean glycated hemoglobin of 9.60% (SD 2.38%), and the prevalence of macrovascular and microvascular disease is shown in Table 1.

Associations of Tyrosine with Type 2 Diabetes Mellitus

In multivariable analysis, tyrosine was associated with type 2 diabetes mellitus in a V-shaped relationship. Obviously, at levels <30 μmol/L, tyrosine was inversely associated with type 2 diabetes mellitus in a roughly linear manner, while at >30 μmol/L, the odds ratio of tyrosine for type 2 diabetes mellitus started to decline gradually, reaching a nadir at 38 μmol/L and then rapidly increasing up to 46 μmol/L. From that point onwards, tyrosine was associated with type 2 diabetes mellitus nearly in a

Table 1 | Clinical and biochemical characteristics of participants according to the occurrence of type 2 diabetes mellitus

Variables	Non- type 2 diabetes mellitus (1,522) Mean/*n* (SD or %)	Type 2 diabetes mellitus (1,032) Mean/*n* (SD or %)	*P*-value
Age (years)	46.3 ± 13.7	57.2 ± 13.8	<0.001
Duration of diabetes (years)		5 (0–10)	
Duration of diabetes ≤2 years		401 (38.9%)	
Male sex	1,131 (74.3%)	549 (53.2%)	<0.001
Weight (kg)	73.6 ± 13.5	70.3 ± 13.2	<0.001
Height (cm)	169.7 ± 8.0	166.5 ± 8.2	<0.001
BMI (kg/m^2)	25.4 ± 3.5	25.3 ± 3.9	0.334
BMI < 18.5	23 (1.5%)	27 (2.6%)	
BMI ≥18.5 and <24	504 (33.1%)	354 (34.3%)	
BMI ≥24 and <28	653 (42.9%)	430 (41.7%)	
BMI ≥ 28	342 (22.5%)	221 (21.4%)	
SBP (mmHg)	130.9 ± 17.2	140.4 ± 24.0	<0.001
DBP (mmHg)	81.0 ± 11.6	82.5 ± 13.5	0.005
HDL-C (mmol/L)	1.55 ± 0.35	1.08 ± 0.35	<0.001
Male (HDL-C <1.0 mmol/L)	54 (3.6%)	224 (21.7%)	<0.001
Female (HDL-C <1.3 mmol/L)	40 (2.5%)	262 (25.4%)	
LDL-C (mmol/L)	3.06 ± 0.70	2.89 ± 1.01	<0.001
Triglyceride (mmol/L)	1.51 (1.02–2.35)	1.67 (1.11–2.38)	0.016
Tyrosine (μmol/L)	42.59 (34.74–52.00)	45.78 (36.70–56.27)	<0.001
<30 μmol/L	170 (11.2%)	102 (9.9%)	<0.001
≥30 to ≤46 μmol/L	745 (48.9%)	424 (41.1%)	
>46 μmol/L	607 (39.9%)	506 (49.0%)	
HbA1c (%)		9.6 ± 2.4	
Macrovascular complications			
Prior CHD		210 (20.4%)	
Prior stroke		199 (19.3%)	
Microvascular complications			
Diabetic retinopathy		162 (15.7%)	
Diabetic nephropathy		188 (18.2%)	
Diabetes medications			
Oral antidiabetic drugs		569 (55.1%)	
Insulin		772 (74.8%)	
Statins		370 (35.9%)	
Other lipid-lowering drugs		23 (2.2%)	
ACEIs		135 (13.1%)	
ARBs		134 (13.0%)	
Other antihypertensive drugs		309 (29.9%)	

Data are mean (standard deviation), median (interquartile range) or *n* (%). ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

linear manner (Figure 1). In the present study, 43.5% (n = 1,113) of participants were categorized into the high level of tyrosine (>46 μmol/L) and 45.5% (n = 506) of the patients with a high tyrosine level had type 2 diabetes mellitus. In contrast, 10.6% (n = 272) of participants had low tyrosine (<30 μmol/L) and 37.5% (n = 102) of the participants who had a low tyrosine level had type 2 diabetes mellitus. If the middle tyrosine levels, that is, ≥30 but ≤46 μmol/L used as the reference, the OR of the high tyrosine for type 2 diabetes mellitus was 1.47 (95% CI 1.24–1.73) in univariable analysis and 1.88 (95% CI 1.44–2.45) in multivariable analysis (Table 2). However, the association between low tyrosine levels and type 2 diabetes mellitus was not statistically significant.

Additive interactions between high/low tyrosine and low HDL-C for type 2 diabetes mellitus

If tyrosine ≤46 μmol/L and high HDL-C (≥1.0 mmol/L in men or ≥1.3 mmol/L in women) were used as the reference, low HDL-C alone, but not high tyrosine alone, was associated with increased OR for type 2 diabetes mellitus in multivariable analysis. The co-presence of both associated factors greatly increased the OR to 54.11 (95% CI 33.96–86.22), with a

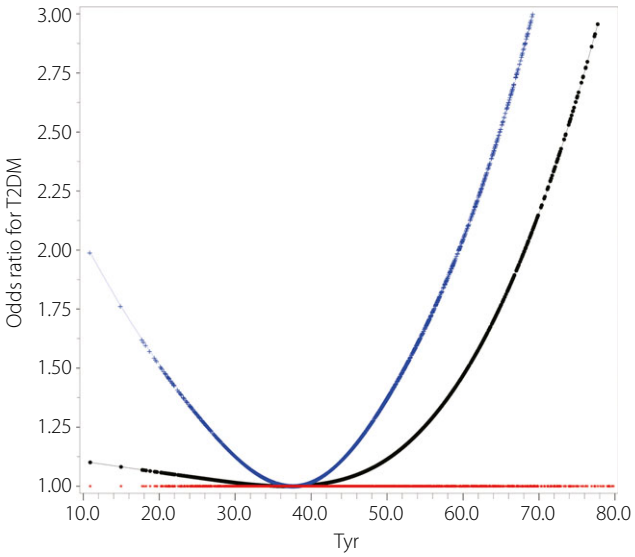

Figure 1 | Odds ratio curves of tyrosine (Tyr) for type 2 diabetes mellitus in Chinese patients. The black curve was derived from univariable analysis, and the blue curve derived from multivariate analysis that adjusted for age, gender, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride. The red curve stands for the reference level (i.e., the odds ratio for type 2 diabetes mellitus was 1).

Table 2 | Odds ratio of tyrosine and additive interaction with lower high-density lipoprotein cholesterol for type 2 diabetes mellitus

	OR (95% CI)	*P*-value
Univariable independent model		
Tyr (per μmol/L)	1.02 (1.01–1.03)	<0.001
Multivariable independent model		
Tyr (per μmol/L)	1.03 (1.02–1.04)	<0.001
Univariable independent model		
<30 μmol/L	1.05 (0.80–1.39)	0.704
≥30 to ≤46 μmol/L	Reference	
>46 μmol/L	1.47 (1.24–1.73)	<0.001
Multivariable independent model†		
<30 μmol/L	1.35 (0.89–2.07)	0.163
≥30 to ≤46 μmol/L	Reference	
>46 μmol/L	1.88 (1.44–2.45)	<0.001
Univariable independent model		
Tyr ≤46 μmol/L & high HDL-C	Reference	
Tyr ≤46 μmol/L & low HDL-C	21.80 (15.68–30.29)	<0.001
Tyr >46 μmol/L & high HDL-C	1.28 (0.98–1.67)	0.072
Tyr >46 μmol/L & low HDL-C	54.35 (35.56–83.07)	<0.001
RERI	32.27 (9.84–54.71)	
AP	0.59 (0.40–0.79)	
S	2.63 (1.56–4.11)	
Multivariable independent model‡		
Tyr ≤46 μmol/L & high HDL-C	Reference	
Tyr ≤46 μmol/L & low HDL-C	18.23 (12.57–26.43)	<0.001
Tyr >46 μmol/L & high HDL-C	1.11 (0.82–1.51)	0.503
Tyr >46 μmol/L & low HDL-C	54.11 (33.96–86.22)	<0.001
RERI	35.78 (11.66–59.89)	
AP	0.66 (0.49–0.83)	
S	3.06 (1.82–5.17)	

†Adjusted for age, sex, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride. ‡Adjusted for age, sex, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride and tyrosine (Tyr) ≤30 μmol/L. Significant elative excess risk due to interaction (RERI) >0, attributable proportion due to interaction (AP) >0 or synergy index (S) >1 indicates a significant additive interaction. HDL-C, high-density lipoprotein cholesterol

significant additive interaction (AP 0.66, 95% CI 0.49–0.83; RERI 35.78, 95% CI 11.66–59.89; and S 3.06, 95% CI 1.82–5.17; Table 2). In contrast, low tyrosine and low HDL-C did not have a significant additive interaction for type 2 diabetes mellitus (Table S1).

Additive interaction between a high level of tyrosine and high triglyceride for type 2 diabetes mellitus

If tyrosine ≤46 μmol/L and low triglyceride were used as the reference, the co-presence of both high triglyceride and high tyrosine was associated with an increased OR for type 2 diabetes mellitus in univariable analysis and multivariable analysis. The additive interaction was not significant (Table S2).

Sensitivity analysis

After exclusion of participants with >2 years of diagnosed diabetes, the co-presence of high tyrosine and low HDL-C led to a larger effect size; that is, the multivariable OR being increased to 60.34 (95% CI 35.17–103.59). Similarly, all the three interaction measures also increased in multivariable analysis (AP 0.72, 95% CI 0.57–0.88; RERI 43.69, 95% CI 13.36–74.02; and S 3.78, 95% CI 2.10–6.83; Table 3).

DISCUSSION

We found that high plasma tyrosine was associated with type 2 diabetes mellitus in Chinese patients with type 2 diabetes mellitus, and tyrosine levels at ≥46 μmol/L were associated with a markedly increased OR of type 2 diabetes mellitus. However, its association with type 2 diabetes mellitus was contingent upon the presence of low HDL-C.

A positive association between tyrosine and the risk of type 2 diabetes mellitus had been repeatedly reported in several studies[9,11,14,24]. A small cross-sectional study of 73 participants who were obese or at high risk for type 2 diabetes mellitus showed that elevated serum tyrosine levels were associated with increased insulin resistance[24]. A large study in 9,000 Finnish men reported that plasma tyrosine was positively associated with glycemia[9]. The Framingham Offspring Studies also found that tyrosine, combined with two other amino acids, was able to predict incident type 2 diabetes mellitus[11]. Consistent with these findings, we observed a positive association between high tyrosine and the increased OR of type 2 diabetes mellitus in

Table 3 | Odds ratio of tyrosine and additive interaction with lower high-density lipoprotein cholesterol for type 2 diabetes mellitus excluding patients with long duration (>2 years)

	OR (95% CI)	*P*-value
Univariable independent model		
Tyr per μmol/L	1.03 (1.02–1.04)	<0.001
Multivariable independent model		
Tyr per μmol/L	1.03 (1.02–1.05)	<0.001
Univariable independent model		
<30 μmol/L	0.86 (0.56–1.30)	0.463
≥30 to ≤46 μmol/L	Reference	
>46 μmol/L	1.63 (1.29–2.05)	<0.001
Multivariable independent model†		
<30 μmol/L	0.76 (0.40–1.44)	0.339
≥30 to ≤46 μmol/L	Reference	
>46 μmol/L	2.22 (1.53–3.16)	<0.001
Univariable independent model		
Tyr ≤46 μmol/L & high HDL-C	Reference	
Tyr ≤46 μmol/L & low HDL-C	19.34 (12.44–30.07)	<0.001
Tyr >46 μmol/L & high HDL-C	1.24 (0.81–1.91)	0.319
Tyr >46 μmol/L & low HDL-C	66.52 (40.36–109.64)	<0.001
RERI	46.93 (16.03–77.83)	
AP	0.71 (0.55–0.86)	
S	3.53 (2.05–6.06)	
Multivariable independent model‡		
Tyr ≤46 μmol/L & High HDL-C	Reference	
Tyr ≤46 μmol/L & Low HDL-C	16.67 (10.34–26.88)	<0.001
Tyr >46 μmol/L & High HDL-C	1.00 (0.63–1.58)	0.989
Tyr >46 μmol/L & Low HDL-C	60.34 (35.17–103.59)	<0.001
RERI	43.69 (13.36–74.02)	
AP	0.72 (0.57–0.88)	
S	3.78 (2.10–6.83)	

†Adjusted for age, sex, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride. ‡Adjusted for age, gender, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride and tyrosine (Tyr) ≤30 μmol/L. Significant relative excess risk due to interaction (RERI) >0, attributable proportion due to interaction (AP) >0 or synergy index (S) >1 indicates a significant additive interaction.

Chinese individuals, although tyrosine in the present participants was significantly lower than those reported in South Asians, even lower than Europeans[13].

Tyrosine is involved in gluconeogenesis and glucose transport. The surplus of tyrosine is rapidly catabolized, which could weaken the clearance of blood glucose and increase gluconeogenesis, and 3-nitrotyrosine formed by the combination of free tyrosine with free radicals could damage pancreatic islet β-cells[25]. Several studies reported that tyrosine metabolism was associated with insulin resistance. Elevated tyrosine might exaggerate pre-existing insulin resistance and also could inhibit the insulin signaling pathway[6,7]. Additionally, tyrosine could be synthesized when the body has enough phenylalanine, which stimulates insulin secretion[26]. In this regard, we found that low tyrosine levels tended to increase the risk of type 2 diabetes mellitus, although not significant. Thus, further prospective cohort studies with large sample sizes are warranted.

The present findings suggested that there was an interactive effect between high tyrosine (>46 μmol/L) and low HDL-C for type 2 diabetes mellitus. It is well established that AMPK plays an important role in energy homeostasis by balancing lipolysis and protein and glycogen storage, which can be triggered by many upstream signals[27]. A mechanistic study found that under the circumstance of hyperglycemia, apolipoprotein A-I gene transcription would be reduced. Apolipoprotein A-I is the major lipoprotein component of HDL, and would affect phosphorylation of AMPK and acetyl-CoA carboxylase[15,28]. It is plausible that the observed interaction might suggest that the association between high tyrosine and type 2 diabetes mellitus is mediated through the AMPK pathway.

The present study had several limitations. First, because of the nature of a retrospective cross-sectional survey, these findings are not evidence of causality between tyrosine and type 2 diabetes mellitus. However, based on consistent findings from previous population-based studies, the present study suggests a strong need to validate these findings in other cohort studies, especially for the selected cut-off points. Second, in our analysis, BMI was associated with type 2 diabetes mellitus in a non-linear manner, and we directly used the spline function of BMI to control its confounding effect in multivariable analysis. However, waist circumference was not available to the analysis and its confounding effect was not adjusted. Third, physical activity and diet in patients with type 2 diabetes mellitus might be different from individuals without diabetes. These data were not collected in this survey and their confounding effects, if any, were not removed. Nevertheless, physical activity and diet were associated with BMI, and careful adjustment for BMI might have partially removed the confounding effect of diet and physical activity. Fourth, inpatients with type 2 diabetes mellitus had more serious disease, and they did not represent general patients with type 2 diabetes mellitus. Our sensitivity analysis showed that exclusion of the patients diagnosed >2 years increased the ORs of the co-presence of both risk factors and the additive interaction measures. Thus, the reported effect sizes of the OR and the additive interaction between high tyrosine and low HDL-C might underestimate their true effect sizes.

The present study has public health importance. China had 113.9 million adults with type 2 diabetes mellitus in 2010, and an increasing number of people are expected to have the devastating disease in the future. It is critically important to accurately predict incident cases at individual levels some years before its onset. However, recent efforts failed to have developed risk scores that can accurately predict incident type 2 diabetes mellitus[5], even inclusion of genetic factors in the predicting tools[29,30]. The present study suggests that high tyrosine, especially combined with low HDL-C, might be a candidate marker for inclusion in future risk scores for type 2

diabetes mellitus in Chinese individuals if these findings can be replicated in cohort studies, especially, in China.

In conclusion, we found that plasma tyrosine levels of >46 μmol/L were associated with a markedly increased odds of type 2 diabetes mellitus in Chinese adults. The association between tyrosine >46 μmol/L and type 2 diabetes mellitus depended on the presence of low HDL-C. As the present findings came from a case–control study, a reverse relationship cannot be excluded. Further follow-up studies are warranted to confirm our novel findings in Chinese people and other populations. If replicated, high tyrosine or the co-presence of high tyrosine and low HDL-C might be included in future risk scores for predicting incident type 2 diabetes mellitus.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Additive interactions between tyrosine <30 μmol/L and with low high-density lipoprotein cholesterol for the risk of type 2 diabetes mellitus.

Table S2 | Additive interactions between tyrosine) >46 μmol/L and high triglyceride for the risk of type 2 diabetes mellitus.