JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Sex-specific differences in blood lipids and lipid ratios in type 2 diabetic foot patients

Shuming Yin[1,†], Puqing Zhao[2,†], Zisheng Ai[3,4,*], Bing Deng[5], Wei Jia[2], Huan Wang[3], Jiaqi Zheng[3]

[1]Division of Gastroenterology, Department of Medicine, Huadong Hospital Affiliated to Fudan University, Shanghai, China, [2]Division of Respiration, Department of Medicine, Shanghai Traditional Chinese Medicine Integrated Hospital Affiliated to Shanghai Traditional Chinese Medicine University, Shanghai, China, [3]Department of Medical Statistics, School of Medicine, Tongji University, Shanghai, China, [4]Shanghai Pudong New Area Mental Health Center, School of Medicine, Tongji University, Shanghai, China, and [5]Division of Cardiology, Department of Medicine, Longhua Hospital Affiliated to Shanghai Traditional Chinese Medicine University, Shanghai, China

Keywords
Diabetic foot, Blood lipids and lipid ratios, Sex differences

***Correspondence**
Zisheng Ai
Tel.: +86-13-774-380-743
Fax: +86-21-6598-6270
E-mail address:
azs1966@126.com

J Diabetes Investig 2021; 12: 2203–2211

doi: 10.1111/jdi.13615

ABSTRACT

Aims/Introduction: Few people have reported whether there are sex differences in blood lipids and lipid ratios in type 2 diabetic foot (T2DF) patients in China. This study attempts to identify the contribution to sex-specific differences in blood lipids and lipid ratios in these patients.

Materials and Methods: In this case–control study, we explore 306 patients with T2DF as the study group and 306 patients with type 2 diabetes mellitus as the control group. Patients were diagnosed according to the Standards of Medical Care in Diabetes–2014 (American Diabetes Association). Blood lipid and lipid ratios were determined according to the National Cholesterol Education Program Adult Treatment Panel III criteria.

Results: We studied male patients with T2DF who were aged 68.00 years (18.00 years) and females who were aged 73.50 years (19.00 years); 61.76% of the patients were men. Men had higher body mass index and glycated hemoglobin levels than women. Compared with type 2 diabetes mellitus patients, T2DF patients had significant differences in total cholesterol/high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol/HDL-C and apolipoprotein (apo)B/apoA-I ratios. HDL-C, triglyceride, apoA-I and apoB/apoA-I ratio showed cardiovascular disease risk in men, whereas total cholesterol, low-density lipoprotein cholesterol, apoB, and the low-density lipoprotein cholesterol/HDL-C and total cholesterol/HDL-C ratios were better predictors in women. The apoB/apoA-I ratio odds ratio values were 2.18 (95% confidence interval 1.17–4.41) and 2.14 (95% confidence interval 1.14–4.00) in male patients with T2DF before and after adjusting for age, respectively ($P < 0.05$).

Conclusions: T2DF patients present sex-specific differences in their blood lipid and lipid ratios, especially in the apoB/apoA-I ratio, which could be a better indicator for cardiovascular disease risk.

INTRODUCTION

Diabetic foot is characterized by foot ulceration, foot neuropathy, and various grades of ischemia and infection in diabetes mellitus patients[1]. A systemic review and meta-analysis in relevant studies[2,3] showed that the global diabetic foot prevalence is 6.3%, and that the Asian prevalence is 5.5%. Similarly, the foot amputation rate in type 2 diabetes patients in China is 19.03%[4]. As a result, type 2 diabetic foot (T2DF) syndrome causes substantial physical, socioeconomic and financial losses[5].

Preceding studies have found that T2DF patients not only have foot ulcers and concomitant infection that might lead to delayed wound healing, but also have higher cumulative rates of lower limb amputation and disability[5]. Therefore, the development of diabetic foot is mainly determined by blood supply disorders; in particular, blood lipids and lipid ratios. Additionally, these patients might suffer from vascular injuries in the heart, brain, kidney and so on. Ultimately, these vascular injuries could result in severe cardiovascular disease (CVD) complications, such as myocardial infarction, stroke and renal failure, which are major causes of mortality in patients with T2DF[6–8]. Furthermore, in the past 10 years, clinical research has shown

[†]Shuming Yin and Puqing Zhao contributed equally to this paper.
Received 16 November 2020; revised 27 May 2021; accepted 10 June 2021

that diabetic foot patients with ulcers have a severe CVD risk with a significant mortality risk. Thus, reducing CVD risk factors has become an important part of diabetic therapy, especially in T2DF patients[9].

Dyslipidemia, specifically low levels of high-density lipoprotein cholesterol (HDL-C) and high levels of low-density lipoprotein cholesterol (LDL-C), has been identified as an independent risk factor for the development in diabetic foot ulcer. Although LDL-C has been widely used to judge the risk of CVD and the response to pharmaceutical treatment[10,11], there is evidence from clinical practice indicating that apolipoproteins are much better predictors of CVD risk than parameters of traditional lipid. Apolipoprotein B (apoB)/apolipoprotein A-I (apoA-I) and not LDL-C/HDL-C ratio has a positive association with clinical CVD events[12].

Previous clinical research on T2DF has mainly focused on closely related metabolic factors, such as systolic blood pressure, diastolic blood pressure, fasting plasma glucose (FPG), postprandial 2-h blood glucose (P2hBG), glycated hemoglobin (HbA1c), total cholesterol (TC), HDL-C, LDL-C, triglyceride (TG), apoB and apoA-I, which have been found to be associated with the onset and development of angiopathy. In recent years, several studies have shown that identifying CVD risk factors in diabetic patients, and monitoring abnormal blood lipids and lipid ratios, such as the TC/HDL-C, LDL-C/HDL-C and apoB/apoA-I ratios, might be beneficial for early detection, diagnosis and treatment in patients with T2DF[13–17]. However, few reports have investigated whether sex is a critical factor in blood lipids and lipid ratios in patients with T2DF.

Therefore, this research was carried out to explore the differences in the concentrations of blood lipids and lipid ratios between male and female T2DF patients. Identifying a sex difference in blood lipids and lipid ratios in T2DF patients might influence lipid-intensive treatment interventions and provide a corresponding theoretical framework for future studies.

MATERIALS AND METHODS

Participants

We carried out a retrospective case–control study from August 2012 to September 2013 with patients in Shanghai Traditional Chinese Medicine Integrated Hospital Affiliated to Shanghai Traditional Chinese Medicine University. Patients with T2DF aged ≥20 years were consecutively invited to participate in medical examinations.

This study was approved by Medical and Life Science Ethics Committee Of Tongji University, No. 2014tjdx16, 5 March 2014, and complied with the documents of the Declaration of Helsinki. All procedures were performed according to the STROBE guideline.

Clinical and biochemical measurements

During the face-to-face interview, information, such as health status, medical treatments and lifestyle risk factors, was collected by physicians. The interviews also included inquiries into history of chronic diseases, such as diagnosis and treatment of type 2 diabetes mellitus, T2DF or hypertension. Individuals in the type 2 diabetes mellitus group frequently used lipid-lowering drugs, such as statins, and antidiabetic drugs, such as insulin, with/without oral hypoglycemic drugs, such as metformin, sulfonylureas and others. These patients were consecutively selected. While type 2 diabetic foot group individual used the above-mentioned measures, at the same time, they used traditional Chinese medicine, such as the QING FA method (which is composed of Chinese herbs with oral and external use), to treat the wound of diabetic foot extremities.

In clinical examinations, blood pressure was measured using an automatic electronic device (OMRON Model HEM-7071; Omron Company, Da Lian, China). Blood pressure was measured three consecutive times at 5-min intervals, after each individual had been placed in a seated position and rested for 30 min. The average value of three measurements was recorded. Height and weight were separately recorded to the nearest 0.1 cm for height and 0.1 kg for weight while patients were wearing light indoor clothing without shoes. Body mass index (BMI) was calculated as weight (kg) divided by squared height (in meters).

After >10 h of overnight fasting in the morning, venous blood samples were collected for measuring the serum lipid profile, FPG, P2hBG and HbA1c. Fasting time was verified before blood specimen collection. Concentrations of fasting serum insulin were discovered by using the electrochemiluminescence assays (Roche Diagnostics, Basel, Switzerland). Homeostasis model assessments of insulin resistance was used to calculate in accordance with the equation described by Matthews[18]. FPG, P2hBG, HbA1c TC, TG, HDL-C, LDL-C, apoB and apoA-I were all measured by using an automatic biochemical instrument (HITACHI Biochemical Autoanalyzer 7600; Tokyo, Japan). The coefficient of variation was 1.00% for FPG, P2hBG, HbA1c and TC; 2.50% for TG; and 3.00% for HDL-C, LDL-C, apoB and apoA-1.

Statistical analysis

Variables were assessed for normal distribution before statistical analysis. If *P*-plots and Kolmogorov–Smirnov tests indicated that variables failed to meet the criteria of normal distribution, then variables were described by using interquartile distances. Consequently, median values are presented for all variables for consistency. Comparisons of continuous variables with normal distributions between and within the T2DF group and type 2 diabetes mellitus group by sex differences were made using *t*-tests or χ^2-tests, and a two-sided *P*-value <0.05 was considered to show statistical significance. If continuous variables did not meet non-normal distributions, comparisons were made using medians and interquartile distances between and within the T2DF group and type 2 diabetes mellitus group by sex differences according to the Mann–Whitney *U*-test, and a two-sided *P*-value <0.05 was considered statistically significant. Subsequently, correlations between the TC/HDL-C, LDL-C/HDL-C and apoB/apoA-I ratios and insulin resistance (IR) by sex

differences were analyzed by using Pearson's or Spearman's correlation coefficients, and regression analyses between and within the T2DF group and type 2 diabetes mellitus group; a two-sided *P*-value <0.05 was considered statistically significant. Finally, within the male and female subgroups, odds ratios (OR) and corresponding 95% confidence intervals (95% CI) were calculated for blood lipids and lipid ratios before and after adjustment of age. The adjusted OR and corresponding 95% CI were estimated using multivariate non-conditional logistic regression analysis models. SPSS (IBM Corp., Armonk, NY, USA) version 20.0 was used for the analysis.

RESULTS

Baseline characteristics of clinical data

A total of 306 T2DF patients and 306 type 2 diabetes mellitus patients without diabetic foot were enrolled in the present study. In Table 1, as all demographic and laboratory variables failed to meet the normal distribution, the median and interquartile range were used for statistical description. Variables, such as age, height, HDL-C and apoA-I, were significantly different between the T2DF group and the type 2 diabetes mellitus group, and between sexes within the T2DF group or the type 2 diabetes mellitus group ($P < 0.05$, Table 1a–c). Diastolic blood pressure, FPG, P2hBG, fasting serum insulin, and homeostasis model assessments of insulin resistance did not differ significantly ($P > 0.05$; Table 1c).

Comparison of blood lipid ratios

In Table 2, the TC/HDL-C, LDL-C/HDL-C and apoB/apoA-I ratios differed significantly by sex differences in the T2DF group ($P < 0.05$). However, the aforementioned three blood lipid ratios were not significantly different by sex differences in the type 2 diabetes mellitus group ($P > 0.05$). There were statistically significant between-group differences in the TC/HDL-C, LDL-C/HDL-C and apoB/apoA-I ratios ($P < 0.001$).

ORs for the blood lipid ratios within the T2DF group

In Table 3, the OR (95% CI) values for TC/HDL-C, LDL-C/HDL-C and apoB/apoA-I ratios were 2.06 (1.30–3.26), 2.30 (1.45–3.65) and 2.86 (1.78–4.52) before adjustment for sex, and 1.33 (1.14–1.55), 1.48 (1.07–2.05) and 2.89 (1.80–4.64) after adjustment for sex, respectively ($P < 0.05$).

ORs of blood lipids and lipid ratios in male patients

In Table 4, among male patients, the OR (95% CI) values for HDL-C, TG, apoA-I and apoB/apoA-I ratio were 0.51 (0.28–0.94), 0.80 (0.63–0.99), 0.30 (0.16–0.56) and 2.18 (1.17–4.41), respectively, before adjustment for age ($P < 0.05$). After adjustment for age, the OR (95% CI) values for HDL-C, TG, apoA-I and apoB/apoA-I ratio were 0.52 (0.28–0.96), 0.77 (0.61–0.97), 0.30 (0.16–0.56) and 2.17 (1.14–4.00), respectively ($P < 0.05$). However, TC, LDL-C, apoB, TC/HDL-C ratio and LDL-C/HDL-C ratio were not significantly different before or after adjustment for age ($P > 0.05$).

ORs of blood lipids and lipid ratios in female patients

In Table 5, female patients had OR (95% CI) values for TC, LDL-C, apoB, TC/HDL-C ratio and LDL-C/HDL-C ratio of 2.41 (1.19–4.89), 4.20 (2.02–8.72), 2.98 (1.43–6.18), 2.92 (1.43–5.96) and 3.58 (1.74–7.38), respectively, before adjustment for age ($P < 0.05$). After adjustment for age, the OR (95% CI) values for TC, LDL-C, apoB, TC/HDL-C ratio and LDL-C/HDL-C ratio were 2.36 (1.15–4.84), 4.17 (1.98–8.81), 2.93 (1.37–6.26), 2.87 (1.39–5.92) and 3.54 (1.70–7.39), respectively ($P < 0.05$). However, HDL-C, TG, apoA-I and the apoB/apoA-I ratio were not significantly different before or after adjustment for age ($P > 0.05$).

DISCUSSION

Numerous studies showed that T2DF patients exhibit vascular injury complications[7,8,19]. Therefore, much attention has recently been given to blood lipids and lipid ratios[16,20–22]. Morbach *et al.*[23] found that diabetic foot patients with amputation and death over a decade were aged 68.8 ± 10.9 years, and male patients accounted for 58.7%. In the present study, 61.76% of male T2DF patients were aged 68.00 years (18.00 years), whereas 38.24% of females were aged 73.50 years (19.00 years). This finding suggests sex-specific differences in T2DF patients, and the younger morbidity of diabetes mellitus in China showed a relationship between BMI and T2DF. After careful analysis of BMI, we found that men weighed more and had higher BMIs than women in both groups, conforming to Peters *et al.*[24] and Humphrey *et al.*[25], and only HbA1c was a useful and significant predictor of developing diabetic foot ulcers. The present study also found that T2DF patients have lower BMIs and worse glucose control than type 2 diabetes mellitus patients. Thus, T2DF patients often have sex-specific CVD risk factors: TC/HDL-C, LDL-C/HDL-C and apoB/apoA-I ratios.

In Table 4, there is a significant difference in the apoB/apoA-I ratio, and no significant difference in the LDL-C/HDL-C ratio in the male patient group. After retrieving from 1 January 2000 to 1 February 2021 in the PubMed database, we did not get any target articles on "type 2 diabetic foot", "apoB/apoA-I", "LDL-C/HDL-C" and "male". Therefore, it is necessary to discuss the possible mechanisms as follows.

First, diabetes mellitus patients without coronary heart disease (CHD) had the same risk of CHD as previous CHD patients without diabetes mellitus[11]. That is, diabetes mellitus patients or CHD patients have equal risk of new CVD, such as myocardial infarction or death in the next decade, peripheral vascular disease, carotid artery lesion or stenosis. Walldius *et al.*[13] and Holme *et al.*[14] drew some conclusions from the Apolipoprotein-related Mortality Risk (AMORIS) study and the AMORIS follow-up study that apoB, LDL-C and TG are all positively related to the risk of fatal myocardial infarction, whereas both HDL-C and apoA-I are negatively correlated with the risk of fatal myocardial infarction. It also definitely proves that the apoB/apoA-I ratio is viewed as the most powerful risk biomarker. The results of the present study show convincingly

Table 1 | Patient characteristics and biochemical markers

(a)

Type 2 diabetic foot group (n = 306)	Median (interquartile range)		Statistics	P-value†
	Male (n = 189)	Female (n = 117)		
Age (years)	68.00 (18.00)	73.50 (19.00)	−2.22	0.026
Weight (kg)	70.00 (15.25)	60.00 (16.05)	−6.00	<0.001
Height (m)	1.70 (0.05)	1.60 (0.06)	−12.25	<0.001
BMI (kg/m^2)	23.44 (3.72)	23.44 (6.08)	−0.03	0.979
SBP (mmHg)	130.00 (15.00)	130.00 (16.25)	−0.29	0.771
DBP (mmHg)	75.00 (10.00)	72.50 (10.00)	−1.15	0.252
TC (mmol/L)	4.04 (1.40)	4.83 (1.63)	−4.22	<0.001
HDL-C (mmol/L)	0.94 (0.28)	1.07 (0.35)	−4.37	<0.001
LDL-C (mmol/L)	2.58 (1.33)	2.86 (1.43)	−2.40	0.016
TG (mmol/L)	1.10 (0.66)	1.49 (1.07)	−4.42	<0.001
ApoB (g/L)	0.79 (0.31)	0.85 (0.35)	−2.42	0.016
ApoA-I (g/L)	1.06 (0.29)	1.23 (0.37)	−4.75	<0.001
FPG, mmol/L	7.40 (4.80)	7.00 (4.55)	−0.40	0.693
P2hBG, mmol/L	12.70 (6.80)	12.80 (6.32)	−0.12	0.907
Fins, μIU/mL	41.02 (63.34)	42.99 (53.79)	−0.57	0.568
HOMA-IR	12.24 (25.12)	13.21 (22.13)	−0.30	0.764
HbA1c (%)	8.10 (2.50)	7.50 (2.70)	−1.83	0.067

(b)

Type 2 diabetes mellitus group (n = 306)	Median (interquartile range)		Statistics	P-value†
	Male (n = 159)	Female (n = 147)		
Age (years)	72.00 (21.00)	78.00 (20.00)	−2.78	0.005
Weight (kg)	70.65 (16.75)	63.00 (13.00)	−6.40	<0.001
Height (m)	1.70 (0.08)	1.58 (0.05)	−12.63	<0.001
BMI (kg/m^2)	24.87 (5.11)	24.67 (4.95)	−0.20	0.843
SBP (mmHg)	130.00 (24.25)	130.00 (23.00)	−0.28	0.780
DBP (mmHg)	80.00 (15.00)	75.00 (10.00)	−1.35	0.176
TC (mmol/L)	4.32 (1.53)	4.34 (1.59)	−1.02	0.310
HDL-C (mmol/L)	0.98 (0.35)	1.09 (0.40)	−3.81	<0.001
LDL-C (mmol/L)	2.69 (1.41)	2.55 (1.23)	−0.11	0.915
TG (mmol/L)	1.16 (0.91)	1.32 (0.91)	−1.44	0.150
ApoB (g/L)	0.77 (0.35)	0.77 (0.29)	−0.20	0.844
ApoA-I (g/L)	1.15 (0.32)	1.25 (0.36)	-4.06	<0.001
FPG (mmol/L)	6.60 (3.00)	7.00 (3.30)	−0.88	0.386
P2hBG (mmol/L)	12.90 (6.00)	13.20 (5.53)	−0.37	0.715
Fins (μIU/mL)	37.15 (66.61)	41.13 (68.63)	0.29	0.769
HOMA-IR	11.06 (22.52)	11.03 (23.25)	−0.22	0.828
HbA1c (%)	7.20 (2.90)	7.35 (2.22)	−0.01	0.995

(c)

Type 2 diabetic foot group vs Type 2 diabetes mellitus group	Statistics	P-value‡
Age (years)	−2.39	0.017
Weight (kg)	−1.55	0.121
Height (m)	−3.49	<0.001
BMI (kg/m^2)	−4.83	<0.001
SBP (mmHg)	−2.70	0.007
DBP (mmHg)	−1.66	0.097
TC (mmol/L)	−0.23	0.818

Table 1 (*Continued*)

(c)

Type 2 diabetic foot group vs Type 2 diabetes mellitus group	Statistics	*P*-value‡
HDL-C (mmol/L)	−2.92	0.004
LDL-C (mmol/L)	−1.90	0.058
TG (mmol/L)	−0.58	0.560
ApoB (g/L)	−1.90	0.058
ApoA-I (g/L)	−4.50	<0.001
FPG (mmol/L)	−1.65	0.100
P2hBG (mmol/L)	−0.03	0.976
Fins (μIU/mL)	−0.07	0.943
HOMA-IR	−0.80	0.422
HbA1c (%)	−3.61	<0.001

†Mann–Whitney test for differences between men and women within the type 2 diabetic foot and type 2 diabetes mellitus groups. ‡Mann–Whitney test for differences between type 2 diabetic foot and type 2 diabetes mellitus groups. ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; BMI, body mass index; DBP, diastolic blood pressure; Fins, fasting serum insulin; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-C, low-density lipoprotein cholesterol; P2hBG, postprandial 2-hour blood glucose; SBP, systolic blood pressure; TC, total cholesterol; TG, triacylglycerol.

Table 2 | Within- and between-group comparisons of blood lipids ratios

Type 2 diabetic foot group (*n* = 306)	Median (interquartile range)			Statistics	*P*-value†
	Men (*n* = 189)	Women (*n* = 117)	Total		
TC/HDL-C ratio	4.50 (1.30)	4.46 (1.45)	4.50 (1.36)	−2.30	0.021
LDL-C/HDL-C ratio	2.75 (1.23)	2.69 (1.11)	2.74 (1.17)	−2.12	0.034
apoB/apoA-I ratio	0.77 (0.35)	0.70 (0.32)	0.74 (0.34)	−2.34	0.019
Type 2 diabetes mellitus group (*n* = 306)	Median (interquartile range)			Statistics	*P*-value†
	Men (*n* = 159)	Women (*n* = 147)	Total		
TC/HDL-C ratio	4.38 (1.56)	3.91 (1.27)	4.06 (1.45)	−0.02	0.983
LDL-C/HDL-C ratio	2.57 (1.43)	2.30 (1.10)	2.41 (1.18)	0.99	0.321
apoB/apoA-I ratio	0.66 (0.28)	0.61 (0.27)	0.64 (0.29)	−0.92	0.358

Type 2 diabetic foot group vs Type 2 diabetes mellitus group	Statistics	*P*-value‡
TC/HDL-C ratio	−3.54	<0.001
LDL-C/HDL-C ratio	−4.21	<0.001
ApoB/apoA-I ratio	−4.69	<0.001

†Mann–Whitney test for differences between men and women within the type 2 diabetic foot and type 2 diabetes mellitus groups. ‡Mann–Whitney test for differences between type 2 diabetic foot and type 2 diabetes mellitus groups. ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; P2hBG, postprandial 2-hour blood glucose; TC, total cholesterol.

that sex differences exist in T2DF. The AMORIS study also showed that the apoB/apoA-I ratio was increased by less than fourfold for men and threefold for women. The results of this study apoB/apoA-I ratio in the T2DF group are similar to the AMORIS study. In addition, Meisinger *et al.*[15] indicated further that the apo B/apo A-I ratio and apo B were important risk factors in the MONICA/KORA Augsburg cohort study, but apoA-I failed to estimate the CVD event risk. This point of view was identified by Sierra-Johnson *et al.*[26] and Sniderman *et al.*[27,28], wherein the apoB/apoA-I ratio and apoB are more accurate and better than the TC/HDL-C and LDL-C/HDL-C ratios. Furthermore, Huang *et al.*[17] found that the apoB/apoA-I ratio (OR 1.19, 95% CI 1.04–1.36) and apoB (OR 1.23, 95% CI 1.00–1.51) are positively and strongly associated with elevated carotid intima-media thickness ($P < 0.0001$) independent of adjustment of risk factors for conventional CVD, such as age and sex. Additionally, Nomikos *et al.*[29] and Kaneva *et al.*[30] showed that the apoB/apoA-I ratio is a better predictor than

Table 3 | Odds ratios for blood lipid ratios in the type 2 diabetic foot group

Type 2 diabetic foot group	Sex-unadjusted Odds ratio (95% CI)	*P*-value	Sex-adjusted Odds ratio (95% CI)	*P*-value
TC/HDL-C ratio	2.06 (1.30–3.26)	0.017	1.33 (1.14–1.55)	<0.001
LDL-C/HDL-C ratio	2.30 (1.45–3.65)	0.004	1.48 (1.07–2.05)	0.004
ApoB/apoA-I ratio	2.86 (1.78–4.52)	<0.001	2.89 (1.80–4.64)	<0.001

ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

Table 4 | Odds ratios values for blood lipids and their ratios in male patients

Blood lipids and their ratios	Age-unadjusted odds ratio (95% CI)	*P*-value	Age-adjusted odds ratio (95% CI)	*P*-value
TC	0.75 (0.41–1.37)	0.355	0.70 (0.38–1.30)	0.258
HDL-C	0.51 (0.28–0.94)	0.031	0.52 (0.28–0.96)	0.037
LDL-C	1.15 (0.63–2.09)	0.652	1.10 (0.60–2.01)	0.766
TG	0.80 (0.63–0.99)	0.047	0.77 (0.61–0.97)	0.024
ApoB	1.07 (0.58–1.97)	0.825	1.01 (0.54–1.87)	0.985
ApoA-I	0.30 (0.16–0.56)	<0.001	0.30 (0.16–0.56)	<0.001
ApoB/apoA-I ratio	2.18 (1.17–4.41)	0.014	2.14 (1.14–4.00)	0.017
TC/HDL-C ratio	1.60 (0.87–2.91)	0.128	1.53 (0.83–2.82)	0.176
LDL-C/HDL-C ratio	1.67 (0.92–3.06)	0.094	1.61 (0.88–2.96)	0.126

ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

Table 5 | Odds ratios values for blood lipids and their ratios in female patients

Blood lipids and their ratios	Age-unadjusted odds ratio (95% CI)	*P*-value	Age-adjusted odds ratio (95% CI)	*P*-value
TC	2.41 (1.19–4.89)	0.015	2.36 (1.15–4.84)	0.019
HDL-C	0.71 (0.35–1.43)	0.331	0.69 (0.34–1.41)	0.309
LDL-C	4.20 (2.02–8.72)	<0.001	4.17 (1.98–8.81)	<0.001
TG	1.09 (0.90–1.33)	0.384	1.08 (0.88–132)	0.462
ApoB	2.98 (1.43–6.18)	0.003	2.93 (1.37–6.26)	0.006
ApoA-I	0.54 (0.26–1.10)	0.087	0.51 (0.25–1.05)	0.069
ApoB/apoA-I ratio	0.53 (0.26–1.07)	0.078	0.54 (0.27–1.11)	0.093
TC/HDL-C ratio	2.92 (1.43–5.96)	0.003	2.87 (1.395.92)	0.004
LDL-C/HDL-C ratio	3.58 (1.74–7.38)	0.001	3.54 (1.70–7.39)	0.001

ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

conventional lipid measurements based on the developed CVD risk hierarchical models in T2DF patients in the ATTICA study, and also a potential plasma atherogenicity biomarker in men with normal lipids aged 20–59 years.

Second, according to the physiological and pathophysiological outcomes of Walldius *et al.*[13,20], apoB as an atherogenic risk predictor results in lipoproteins infiltrating the artery walls and it combines with its receptor, causing uptake of more cholesterol in peripheral tissues. More apoB, meaning an increase in small, dense LDL, might play a key role in oxidization and grow vascular plaques with an inflammatory response. Excessive cholesterol in peripheral tissues might be collected by apoA-I back to HDL-C in the liver. Therefore, apoA-I has anti-inflammatory and anti-oxidant effects. Therefore, the apoB/apoA-I ratio simply means balanced cholesterol transport. Huang *et al.*[17] also found that on the basis of the atherosclerosis hypothesis of response to retention, the essential commencing atherosclerosis process is apoB lipoprotein retention in the subendothelial region, which results in a chronic inflammatory response with weak macrophages and T cells that initiates the subsequent development of the lesion. Additionally, Sierra-Johnson *et al.*[31] verified that a higher apoB/apoA-I ratio (men: OR 4.12, 95% CI 1.97–8.81; women: OR 3.69, 95% CI 1.94-7.27) had an independent significant association with insulin resistance (men: $R^2 = 0.09$, $P < 0.001$; women: $R^2 = 0.05$, $P < 0.001$) in the USA population without diabetes mellitus.

Insulin resistance with metabolic risk factors clustering together is the primary potential pathophysiological disorder that leads to dyslipidemia, hypertension, diabetes mellitus, the state of prothrombogenesis and proinflammation, which gives rise to increased CVD risk. Nehring *et al.*[32] proved that elderly type 2 diabetes mellitus patients (OR 0.94, 95% CI 0.92–0.96, $P = 0.00001$), male (OR 2.83, 95% CI 1.86–4.28, $P = 0.00001$), hyperlipidemia (OR 0.54, 95% CI 0.36–0.81, $P = 0.01$) and so on are risk factors for the occurrence and development of diabetic foot.

Third, Walldius *et al.*[20] confirmed that the apoB/apoA-I ratio was a target for lipid-lowering therapy, which produces a better effect on apoB decreasing by 15–50% and apoA-I increasing by 5–15%. ApoB/apoA-I ratio values were connected with a reduction in CVD events. Taskinen *et al.*[33] noted that the apoB/apoA-I ratio could provide more evidence for replacement of LDL-C/HDL-C and TC/HDL-C ratios as a predictive risk factor or as a useful potential management of lipid monitoring in clinical practice. The results of the present study in the apoB/apoA-I ratio in T2DF patients coincide with the findings of Taskinen *et al.*[33] Furthermore, Ahmed *et al.*[34] discovered that the apoB/apoA-I ratio and apoA-I were significantly associated with physical activity measures objectively evaluated in elderly individuals. In addition, a lower apoB/apoA-I ratio and a higher apoA-I level might be associated with higher levels of physical activity, and paying more attention to the apoB/apoA-I ratio in male T2DF patients after exercise might be beneficial in the future.

As shown in Table 5, there was no significant difference in the OR of the apo B/apo A-I ratio, and there was a significant difference in the LDL-C/HDL-C ratio. While searching from 1 January 2000 to 1 February 2021 in the PubMed database, we still did not obtain any study on "type 2 diabetic foot", "apoB/apoA-I", "LDL-C/HDL-C" and "female". Therefore, it is necessary to discuss the possible causes as follows.

First, Holme *et al.*[15] accepted the apoB/apoA-I ratio: 0–7.0. Several cited references to this paper referred to the LDL/HDL-C ratio without definite range values. However, Zhao *et al.*[22] showed that according to the LDL-C/HDL-C ratio assessing arterial stiffness by brachial-ankle pulse wave velocity in middle-aged and elderly Chinese individuals, there was a significant difference between men and women (2.53 ± 0.84 vs 2.39 ± 076, $P = 0.005$). In addition, according to brachial-ankle pulse wave velocity tertiles, there is no significant difference in T1, T2 and T3 in women (2.26 ± 0.71, 2.47 ± 0.71 vs 2.44 ± 0.72, $P = 0.012$), and there is no significant difference in that in men (2.35 ± 0.78, 2.48 ± 0.90 vs 2.58 ± 0.78, $P = 0.158$). Therefore, the LDL-C/HDL-C ratio is a better risk marker in female middle-aged and elderly Chinese individuals using brachial-ankle pulse wave velocity to estimate arterial stiffness.

Second, according to the physiological and pathophysiological outcomes of Walldius *et al.*[20], LDL-C was a significant risk factor, whereas HDL-C was a significant protective factor. Therefore, increased LDL-C/HDL-C ratios were connected with CVD events. Tangvarasittichai *et al.*[35] insisted that there was a significant difference in the LDL/HDL ratio between male and female type 2 diabetes mellitus patients (2.89 [2.38–3.28] vs 2.11 [1.51–2.69], $P = 0.001$). Sniderman *et al.*[28] showed that in addition to heterozygous ABCA1 mutations, macrophage-induced inflammation of the coronary artery might be the predominant risk factor detected with low HDL. Significant cholesterol accumulation in peripheral tissues and arteries is linked with the absence of HDL. LDL injures and penetrates the arterial endothelium, and causes cholesterol deposits in the arterial wall, which lead to thrombogenesis. LDL is present in every stage of vascular disease, and the effects of HDL rely on the concurrence of LDL during the process of atherogenesis. In summary, the contingent role of HDL is opposite to the causal role of LDL during the process of atherogenesis.

Third, Ahmed *et al.*[34] confirmed that physical activity is a healthy behavior for favorable action on the apoB/apoA-I ratio and apo A-I, which improves limited catabolite HDL production, insulin resistance and blood pressure, and decreases the quantity of LDL and VLDL.

The present study has several limitations: (i) after retrieving articles by searching under "Mesh Major Topic" the terms "type 2 diabetic foot", "arteriosclerosis" and "smoking" from 1 January 2000 to 1 April 2021 in the PubMed database, we obtained 1,391, 96,722 and 52,785 results, respectively. However, when combining "arteriosclerosis" with "smoking" as "Mesh Major Topic" to target articles, we had 477 results. Then, when retrieving using "type 2 diabetic foot", "arteriosclerosis" and "smoking" as "Mesh Major Topic" to target articles, we found no results; and (ii) after reviewing the raw data in the present study, we found there was <10% data involved in smoking. Therefore, insufficient candidates cannot support the effects of smoking statistically. Although this question has no retrieving results now, it still encourages us to continue this study to fulfil the effects of smoking in the future.

In conclusion, T2DF patients with CVD risk factors have sex-specific differences in blood lipids and lipid ratios in China. In men, risk factors include HDL-C, TG, apoA-I and the apoB/apoA-I ratio, whereas in women, TC, LDL-C, apoB, LDL/HDL-C ratio and TC/HDL-C ratio are better predictors of CVD. The sex-specific differences hinted that male patients with T2DF mainly have metabolic and transportable disorders of HDL-C, TG and their apolipoprotein ratios, whereas female patients with T2DF mainly have conventional disorders of blood lipids. Furthermore, the present study results suggest that the apoB/apoA-I ratio might be a more clinically meaningful index for male patients with T2DF in predicting the risk of CVD. Thus, through the early assessment of sex-specific blood lipids and lipid ratios in patients with T2DF, we should adopt corresponding interventions or treatments, and further study of the sex-specific differences between blood lipids and lipid ratios in T2DF patients is required.

ACKNOWLEDGMENTS

This study was supported by the following foundations: National Natural Science Foundation of China (Grant No.81872718); Shanghai Municipal Health and Family Planning Commission (Grant No.201840041); The Outstanding Clinical Discipline Project of Shanghai Pudong (Grant No. PWYgy2018-10); and Key Undergraduate Course Project of Shanghai Education Commission (201965-2). The authors thank the participants for their cooperation.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Palumbo PJ, Melton LJ. Peripheral vascular disease and diabetes. In: Harris MI, RF Hamman (ed). Diabetes in America, 1st edn. Washington, DC: US Government Printing Office, 1985.
2. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2014; 37: S14–80.
3. Zhang P, Lu J, Jing Y, *et al*. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. *Ann Med* 2017; 49: 106–116.
4. Jiang Y, Ran X, Jia L, *et al*. Epidemiology of type 2 diabetic foot problems and predictive factors for amputation in China. *Int J Low Extr Wound* 2015; 14: 19–27.
5. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA* 2005; 293: 217–228.
6. Speckman RA, Frankenfield DL, Roman SH, *et al*. Diabetes is the strongest risk factor for lower-extremity amputation in new hemodialysis patients. *Diabetes Care* 2004; 27: 2198–2203.
7. Pinto A, Tuttolomondo A, Di Raimondo D, *et al*. Ischemic stroke in patients with diabetic foot. *Int Angiol* 2007; 26: 266–269.
8. Faglia E, Clerici G, Clerissi J, *et al*. Long-term prognosis of diabetic patients with critical limb ischemia: a population-based cohort study. *Diabetes Care* 2009; 32: 822–827.
9. Young MJ, McCardle JE, Randall LE, *et al*. Improved survival of diabetic foot ulcer patients 1995–2008: possible impact of aggressive cardiovascular risk management. *Diabetes Care* 2008; 31: 2143–2147.
10. De Backer G, Ambrosioni E, Borch-Johnsen K, *et al*. European guidelines on cardiovascular disease prevention in clinical practice. Third joint task force of European and other societies on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2003; 24: 1601–1610.
11. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001; 285: 2486–2497.
12. Simon A, Chironi G, Levenson J. Comparative performance of subclinical atherosclerosis tests in predicting coronary heart disease in asymptomatic individuals. *Eur Heart J* 2007; 28: 2967–2971.
13. Walldius G, Jungner I, Holme I, *et al*. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet* 2001; 358: 2026–2033.
14. Holme I, Aastveit AH, Jungner I, *et al*. Relationships between lipoprotein components and risk of myocardial infarction: age, gender and short versus longer follow-up periods in the Apolipoprotein MOrtality RISk study (AMORIS). *J Intern Med* 2008; 264: 30–38.
15. Meisinger C, Loewel H, Mraz W, *et al*. Prognostic value of apolipoprotein B and A-I in the prediction of myocardial infarction in middle-aged men and women: results from the MONICA/KORA Augsburg cohort study. *Eur Heart J* 2005; 26: 271–278.
16. Holzmann MJ, Jungner I, Walldius G, *et al*. Dyslipidemia is a strong predictor of myocardial infarction in subjects with chronic kidney disease. *Ann Med* 2012; 44: 262–270.
17. Huang F, Yang Z, Xu B, *et al*. Both serum apolipoprotein B and the apolipoprotein B/apolipoprotein A-I ratio are associated with carotid intima-media thickness. *PLoS One* 2013; 8: e54628.
18. Matthews DR, Hosker JP, Rudenski AS, *et al*. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28: 412–419.
19. Reiber GE. The epidemiology of diabetic foot problems. *Diabet Med* 1996; 13: S6–11.
20. Walldius G, Jungner I. The apoB/apoA-I ratio: a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy–a review of the evidence. *Intern Med* 2006; 259: 493–519.
21. Reiner Z, Catapano AL, De Backer G, *et al*. ESC/EAS Guidelines for the management of dyslipidaemias The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Atherosclerosis* 2011; 217: 3–46.
22. Zhao W, Gong W, Wu N, *et al*. Association of lipid profiles and the ratios with arterial stiffness in middle-aged and elderly Chinese. *Lipids Health Dis* 2014; 13: 37.
23. Morbach S, Furchert H, Groblinghoff U, *et al*. Long-term prognosis of diabetic foot patients and their limbs: amputation and death over the course of a decade. *Diabetes Care* 2012; 35: 2021–2027.
24. Peters EJ, Armstrong DG, Lavery LA. Risk factors for recurrent diabetic foot ulcers: site matters. *Diabetes Care* 2007; 30: 2077–2079.
25. Humphrey ARG, Dowse GK, Thoma K, *et al*. Diabetes and nontraumatic lower extremity amputations: incidence, risk factors, and prevention—a 12-year follow-up study in Nauru. *Diabetes Care* 1996; 19: 710–714.

26. Sierra-Johnson J, Fisher RM, Romero-Corral A, *et al*. Concentration of apolipoprotein B is comparable with the apolipoprotein B/apolipoprotein A-I ratio and better than routine clinical lipid measurements in predicting coronary heart disease mortality: findings from a multi-ethnic US population. *Eur Heart J* 2009; 30: 710–717.
27. Sniderman AD, Jungner I, Holme I, *et al*. Errors that result from using the TC/HDL C ratio rather than the apoB/apoA-I ratio to identify the lipoprotein-related risk of vascular disease. *J Intern Med* 2006; 259: 455–461.
28. Sniderman AD, Kiss RS. The strengths and limitations of the apoB/apoA-I ratio to predict the risk of vascular disease: a Hegelian analysis. *Curr Atheroscler Rep* 2007; 9: 261–265.
29. Nomikos T, Panagiotakos D, Georgousopoulou E, *et al*. Hierarchical modelling of blood lipids' profile and 10-year (2002–2012) all cause mortality and incidence of cardiovascular disease: the ATTICA study. *Lipids Health Dis* 2015; 14: 108.
30. Kaneva AM, Potolitsyna NN, Bojko ER, *et al*. The apolipoprotein B/apolipoprotein A-I ratio as a potential marker of plasma atherogenicity. *Dis Markers* 2015; 591454.
31. Sierra-Johnson J, Romero-Corral A, Somers VK, *et al*. ApoB/apoA-I ratio: an independent predictor of insulin resistance in US non-diabetic subjects. *Eur Heart J* 2007; 28: 2637–2643.
32. Nehring P, Mrozikiewicz-Rakowska B, Krzyżewska M, *et al*. Diabetic foot risk factors in type 2 diabetes patients: a cross-sectional case control study. *J Diabetes Metab Disord* 2014; 13: 79.
33. Taskinen M-R, Barter PJ, Ehnholm C, *et al*. Ability of traditional lipid ratios and apolipoprotein ratios to predict cardiovascular risk in people with type 2 diabetes. *Diabetologia* 2010; 53: 1846–1855.
34. Ahmed K, Rask P, Hurtig-Wennlof A. Serum apolipoproteins, apoB/apoA-I ratio and objectively measured physical activity in elderly. *Scand Cardiovasc J* 2011; 45: 105–111.
35. Tangvarasittichai S, Poonsub P, Tangvarasittichai O. Association of serum lipoprotein ratios with insulin resistance in type 2 diabetes mellitus. *India J Med Res* 2010; 131: 641–648.