Associations of Insulin Resistance and Beta Cell Function with Abnormal Lipid Profile in Newly Diagnosed Diabetes: A Cross-sectional Study

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Original investigation

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Abstract

Background: Abnormal lipids are strong predictive factors of cardiovascular disease (CVD) in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). However, the potential associations of insulin resistance (IR) and beta cell function (BCF) in diabetes and abnormal lipids, i.e. high triglyceride (TG), low high-density lipoprotein cholesterol (HDL-C) and high low-density lipoprotein cholesterol (LDL-C) are not fully understood. In this study, we aim to explore whether decreased BCF and increased IR in newly diagnosed T1DM or T2DM are associated with abnormal lipids.

Methods: Clinical and laboratory data were collected from 16334 adults with newly diagnosed diabetes in this cross-sectional study. Types of diabetes were diagnosed based on clinical characteristics and diabetes-related biochemical measurement results. Homeostasis model assessment were used to estimate IR and BCF. Restricted cubic spline and binary logistic regression were used to examine the associations of IR or BCF and abnormal lipids in T1DM and T2DM, respectively.

Results: High TG, low HDL-C and high LDL-C accounted for 49.7%, 47.7% and 59.2%, respectively. In multivariable analysis, high IR was associated with increased risk of high TG (Odds ratios (ORs) of homeostasis model assessment of insulin resistance (HOMA2-IR) ≥2, ≥1-<2 vs <1: 4.77, 95% CI 2.69-8.57; 2.31, 95% CI 1.54-3.47, p for trend < 0.001) in T1DM and was associated with elevated risk of high TG, low HDL-C and high LDL-C (all p for trend <0.01) in T2DM. Low BCF, i.e., homeostasis model assessment of beta-cell function (HOMA2-B) <30 versus ≥30, was associated with marginally increased risk of high TG (OR 1.42, 95% CI 0.98-2.10, p = 0.07) in T1DM and associated with increased risk of high TG (OR 1.21, 95% CI 1.09-1.34, p <0.001) and high LDL-C (OR 1.23, 95% CI 1.12-1.36, p <0.001) in T2DM.

Conclusions: In patients with newly diagnosed diabetes, high IR and low BCF had different associations with risk of dyslipidemia in T1DM and T2DM, suggesting that early treatment that improve IR or BCF may have a benefit for abnormal lipid metabolism.

Introduction

Cardiovascular disease (CVD), as one of the most severe complications, is the leading cause of death in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) [1, 2]. It is established that some lipid components such as high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C), are risk factors for diabetes. On the other hand, abnormal lipids are highly predictive of CVD in patients with diabetes [3, 4]. Disorders in carbohydrate metabolism in diabetes can cause or worsen abnormal lipid metabolism in numbers of ways. In both T1DM and T2DM, poor glycemic control can increase serum levels of TG and low-density lipoprotein cholesterol (LDL-C), and decreases levels of HDL-C [5]. Indeed, it is essential to understand biological links between diabetes and lipid abnormalities for further reduction in increased burden of CVD in patients with diabetes.

Pathophysiologically, insulin resistance (IR) and decreased beta cell dysfunction are two major contributors to diabetes. Interactions between IR and pancreatic beta cell function (BCF) play a key role in the pathogenesis of both T1DM and T2DM [6]. T1DM mainly arises from beta cell function impairment while T2DM results from insulin resistance along with inadequate beta cell function [7]. The decreased beta cell function and insulin resistance in diabetes may also play a key role in worsened lipid metabolism. In this connection, insulin

deficiency or insulin resistance can increase TG by reducing the suppression of TG lipolysis and increasing fatty acids in the liver, and decrease HDL-C by reducing the inhibition of ApoA-I expression needed for HDL formation [8]. However, it remains unknown which of decreased BCF or increased IR contributes most to abnormal metabolism in different lipid components, i.e., high TG, low HDL-C and high LDL-C.

Statin treatment was associated with a 37% reduction in major CVD events in individuals with T2DM [9], but the residual risk of CVD remains substantially high. It is needed to understand the associations of the two fundamental features of diabetes, decreased BCF and increased IR, for different abnormal lipid components so as better control of CVD risk factors. Therefore, we conducted a cross-sectional study in China and aimed to explore whether decreased BCF and increased IR in newly diagnosed T1DM or T2DM are associated with abnormal lipids, i.e., high TG, low HDL-C and high LDL-C, with use of restricted cubic spline (RCS) to detect these potential non-linear associations.

Methods

Study design and population

From April 2015 to October 2017, we conducted a nationwide, multi-center, cross-sectional survey of 18, 976 participants with newly diagnosed diabetes in China. In this survey, we invited forty-six tertiary care hospitals across all seven geographic regions of China from twenty provinces and four municipalities to participate in this cross sectional survey. The Ethics Committees of the Second Xiangya hospitals, Central South University, China, approved this study, and all patients provided written informed consent before data collection.

The inclusion criteria were set as: 1) diagnosis of diabetes based on the World Health Organization 1999 criteria; 2) age 18 years and older; 3) diabetes duration less than one year; 4) outpatients attending clinics in the department of endocrinology. Individuals were excluded if pregnant at the time of diabetes diagnosis, if they had gestational diabetes mellitus, or if they had co-existing acute diseases such as infection or acute myocardial infarction that could affect glucose metabolism. In addition, we excluded 62 cases with insufficient data for disease classification, 1635 cases missing lipid data and 945 cases missing homeostasis model assessment of insulin resistance (HOMA2-IR) or beta-cell function (HOMA2-B) data. The remaining 16,334 patients were included in this analysis (Fig. 1).

Data collection procedures

Demographic characteristics (i.e., age and sex), clinical features, and lifestyle risk factors (i.e., exercise habits, diet, smoking, and alcohol consumption) were collected using a standard questionnaire by research nurses at each of the 46 participating hospitals. The nurses used standardized procedures to measure height, weight, waist circumference, hip circumference, systolic blood pressure (SBP) and diastolic blood pressure (DBP). Drug use information was retrieved from case notes.

Laboratory assays

Fasting plasma glucose (FPG), total cholesterol, triglycerides, HDL-C, LDL-C, plasma hemoglobin A1c (HbA1c) and fasting C-peptide were assayed by standard methods at the study sites. Postprandial blood samples were tested for 2-h postprandial plasma glucose (PPG) and C-peptide. The core laboratory (Central South University) performed serum glutamic acid decarboxylase antibodies (GADA) assays by a standardized radioligand assay

as reported [10]. Serum samples for GADA assays from other hospitals were shipped on ice within one day and stored at -80 °C in the core laboratory. The assay was assessed in the 2016 islet autoantibody standardization program (IASP 2016).

Classification of diabetes

The classification of T1DM and T2DM were based on clinical characteristics and diabetes-related biochemical measurement results, including fasting and 2-hour postprandial plasma glucose and C-peptide, lipids levels, HbA1c and GADA serum levels. Type 1 diabetes was diagnosed based on insulin-dependent diabetes, prone to ketoacidosis or presence of GADA positivity. Type 2 diabetes was diagnosed as GADA-negative and insulin-independent patients.

Evaluation of insulin resistance and beta cell function

HOMA2-IR and HOMA2-B are estimated based on C peptide levels and plasma glucose using the HOMA calculator [11].

Definition of dyslipidemia

As recommended by the American Diabetes Association (ADA) [12], high TG was defined as TG ≥ 1.7 mmol/L, low HDL-C was defined as HDL-C < 1.0 mmol/L (males) and < 1.3 mmol/L (females), and high LDL-C was defined as LDL-C ≥ 2.6 mmol/L.

Statistical analysis

Continuous variables were expressed as mean ± (standard deviation, SD) or median (interquartile range) based on evaluation of normal distribution; categorical variable were given as number (percent). For analysis of continuous variables, Student t test or Mann-Whitney test were performed to compare differences between groups where appropriate. Frequency differences were compared using Chi-square test. R (version 4.0.2) and SPSS (version 26) were used to perform all the analysis. $p < 0.05$ was considered statistically significant.

Because there are no data to suggest that HOMA-B and HOMA-IR were linearly associated with abnormal lipids in diabetes, RCS analyses nested in the multivariable logistic regression analyses were used to check full-range associations of HOMA2-IR and HOMA2-B with different dyslipidemia in T1DM and T2DM, respectively. We first performed univariable analysis and then multivariable analyses with adjustment for age, sex, current smoking, current drinking, body mass index (BMI, calculated as kg/m^2), HbA1c, SBP and current use of drugs including lipid lowering treatment, oral anti-diabetic treatment and insulin treatment to obtain full-range associations of HOMA2-IR and HOMA2-B with different dyslipidemia in T1DM and T2DM. In the RCS analysis, four knots were chosen because four knots were able to offer an adequate fit of the model and represents a good compromise between flexibility and the loss of precision caused by overfitting a small sample [13]. We identified threshold points of HOMA2-IR and HOMA2-B at the points, if any, where dyslipidemia risk started to rise or fall sharply, as in the previous investigations [14].We further stratified HOMA2-IR and HOMA2-B at the identified cutoff points and repeated the univariable and multivariable analysis to obtain odds ratios (OR) and 95% confidence intervals (CI) of HOMA2-IR and HOMA2-B in categorical variables as stratified at the these threshold points for high TG, low HDL-C and high LDL-C among patients with T1DM and T2DM, respectively.

Results

Characteristics of the study participants

The mean age of the patients was 50.3 ± 13.3 years. Patients with T1DM were significantly younger, leaner and they had lower blood pressure, better lipid metabolic parameters but higher FPG and HbA1c levels than those with T2DM. Patients with T1DM were less insulin-resistant and less likely to have diet treatment, to be engaged in exercise and to have lipid lowering treatment than those with T2DM (Table 1).

Table 1
Characteristics of the study participants

Characteristics	T1DM	T2DM	p
n	1187	15147	
Age (years)	42.9 ± 14.8	50.9 ± 13.0	< 0.001
Male (n,%)	697 (58.7%)	9078 (59.9%)	0.412
BMI (kg/m^2)	21.8 ± 3.7	24.8 ± 3.6	< 0.001
FPG (mmol/L)	9.4 ± 4.2	9.1 ± 3.5	0.002
HbA1c (%)	10.7± 3.2	9.4 ± 2.7	< 0.001
Systolic BP (mmHg)	121.0 ± 15.8	127.8 ± 16.3	< 0.001
Diastolic BP (mmHg)	76.5 ± 10.7	80.2 ± 10.5	< 0.001
Waist circumference (cm)	81.3 ± 10.5	88.4 ± 10.6	< 0.001
PPG (mmol/L)	16.7 ± 6.6	15.3 ± 3.7	< 0.001
Triglyceride (mmol/L)	1.2 (0.8–1.8)	1.7 (1.2–2.7)	< 0.001
Triglyceride > 1.7 mmol/L (n,%)	344 (29.0%)	7770 (51.3%)	< 0.001
Total Cholesterol (mmol/L)	4.5 ± 1.3	4.8 ± 1.3	< 0.001
LDL-C (mmol/L)	2.7 ± 1.0	2.9 ± 1.0	< 0.001
LDL-C > 2.6 mmol/L (n,%)	599 (50.5%)	9078 (59.9%)	< 0.001
HDL-C (mmol/L)	1.2 (1.0-1.5)	1.1 (0.9–1.3)	< 0.001
HDL-C < 1.0 mmol/L, male, < 1.3 mmol/L female (n,%)	466 (39.3%)	7318 (48.3%)	< 0.001

Note: Data are presented as mean± SD, median (interquartile range), or n (%).

Abbreviation: BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; BP, blood pressure; PPG, postprandial plasma glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Comparisons between groups were performed with Mann-Whitney test or t test for continuous variables depending on normal distribution and chi-square test for categorical variables.

Characteristics	T1DM	T2DM	p
Family history of diabetes (n,%)	280 (24.0%)	4310 (29.1%)	< 0.001
Fasting C-peptide (nmol/L)	200 (83.3–410.0)	569.4 (366.3–810.0)	< 0.001
Postprandial C-peptide (nmol/L)	423.5 (160.0-965.7)	1435.2 (879.9-2243.4)	< 0.001
HOMA2-IR	0.57 (0.22–1.17)	1.5 (1.0-2.2)	< 0.001
HOMA2-B (%)	20.2 (8.1–39.9)	43.9 (24.5–70.1)	< 0.001
Current smoking (n,%)	359 (30.7%)	4482 (30.0%)	0.611
Current drinking (n,%)	160 (13.8%)	2651 (17.9%)	< 0.001
Diet treatment (n,%)	551 (53.8%)	6929 (61.8%)	< 0.001
Physical activity (n,%)	453 (44.2%)	5914 (52.8%)	< 0.001
Lipid lowering drugs (n,%)	66 (6.1%)	1645 (12.3%)	< 0.001
Insulin treatment (n,%)	298 (25.5%)	1187 (8.0%)	< 0.001
Note: Data are presented as mean± SD, median (interquartile range), or n (%).			
Abbreviation: BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; BP, blood pressure; PPG, postprandial plasma glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.			
Comparisons between groups were performed with Mann-Whitney test or t test for continuous variables depending on normal distribution and chi-square test for categorical variables.			

S- or U-shaped associations between HOMA2-IR or HOMA2-B and the risk of dyslipidemia in T1DM and T2DM

We modeled the associations of HOMA2-IR and HOMA2-B with the risk of dyslipidemia using RCS models in T1DM and T2DM after adjustment for age, sex, HOMA2-IR (or HOMA-B where appropriate), current smoking, current drinking, BMI, HbA1c, SBP, lipid lowering treatment, oral anti-diabetic treatment and insulin treatment (Fig. 2, Fig. 3).

The associations of HOMA2-IR and the risks of dyslipidemia (high TG, low HDL-C and high LDL-C) were S-shaped in T1DM with a positively linear association when HOMA2-IR was between 0.5 to 1.5-2.0 (Fig. 2a-c). However, in patients with T2DM, HOMA2-IR was positively associated with the risk of dyslipidemia when HOMA2-IR < 3.0 and

levelled off for the risk of high TG and low HDL-C but showed a negative association with the risk of high LDL-C when HOMA2-IR > 3.0 (Fig. 2d-f).

The associations of HOMA2-B and the risk of dyslipidemia were different in T1DM as compared to those in T2DM. In patients with T1DM, there was a U-shaped association between HOMA2-B and the risk of high TG and high LDL-C with the lowest risk related to HOMA2-B of about 40.0 to 60.0 (Fig. 3a,3c). HOMA2-B was linearly positively associated with the risk of low HDL-C in T1DM (Fig. 3b). In patients with T2DM, however, the risk was stable at first and started to fall (for high TG) or rise (for low HDL-C) after HOMA2-B > 30 (Fig. 3d,3e). HOMA2-B was negatively associated with the risk of high LDL-C when less than 80 and then stable afterwards (Fig. 3f).

From above, the risk of abnormal lipid started to change steeply mainly from 1 to 2 of HOMA2-IR and at 30.0 and downwards of HOMA2-B, therefore, we selected these values as threshold points for further logistic regression analysis.

Associations between HOMA2-IR and the risk of dyslipidemia in T1DM and T2DM

The risks of dyslipidemia (high TG, low HDL-C and high LDL-C) associated with HOMA2-IR were estimated by both univariate logistic regression and multivariable logistic regression with adjustment for age, sex, beta cell function categories, current smoking, current drinking, BMI, HbA1c, SBP, lipid lowering treatment, oral anti-diabetic treatment and insulin treatment in T1DM and T2DM (Table 2). In patients with T1DM, high HOMA2-IR was associated with an elevated risk of high TG (p for trend < 0.001), low HDL-C (p for trend = 0.012) and high LDL-C (p for trend = 0.003) in univariable regression models but was only associated with increased risk of high TG (ORs of HOMA2-IR ≥ 2, ≥1-<2 vs < 1: 4.77, 95% CI 2.69–8.57; 2.31, 95% CI 1.54–3.47, p for trend < 0.001) after adjustment for potential confounders (Table 2). In patients with T2DM, high HOMA2-IR was associated with an elevated risk of high TG, low HDL-C and high LDL-C (all p for trend < 0.001) in univariable regression models and remained significant for high TG (ORs of HOMA2-IR ≥ 2, ≥1-<2 vs < 1: 2.80, 95% CI: 2.49–3.15; 1.71, 95% CI 1.54–1.89, p for trend < 0.001), low HDL-C (ORs of HOMA2-IR ≥ 2, ≥1-<2 vs < 1: 1.54, 95% CI 1.38–1.74; 1.21, 95% CI 1.09–1.34, p for trend < 0.001) and high LDL-C (ORs of HOMA2-IR ≥ 2, ≥1-<2 vs < 1: 1.19, 95% CI 1.06–1.33; 1.10, 95% CI 0.99–1.21, p for trend = 0.004) after adjustment for potential confounders (Table 2).

Table 2
Odds ratio of insulin resistance for abnormal lipid profile in T1DM and T2DM

Insulin resistance	High TG			Low HDL-C			High LDL-C		
	n (%)	OR (95% CI)	p	n (%)	OR (95% CI)	p	n (%)	OR (95% CI)	p
Univariable									
T1DM			< 0.001ζ			0.012 ζ			0.003 ζ
High(≥ 2)	67 (59.8%)	6.11 (3.92–9.61)	< 0.001	55 (49.1%	1.60 (1.05–2.45)	0.03	69 (61.6%	1.85 (1.21–2.85)	0.005
Median(≥ 1-<2)	95 (37.8%	2.36 (1.71–3.26)	< 0.001	110 (43.8%)	1.32 (0.97–1.78)	0.07	134 (53.4%)	1.29 (0.96–1.74)	0.09
Low(< 1)	182 (22.1%)	Ref		301 (36.5%	Ref		396 (48.1%	Ref	
T2DM			< 0.001 ζ			< 0.001 ζ			< 0.001 ζ
High(≥ 2)	3024 (65.3%)	3.47 (3.17–3.81)	< 0.001	2599 (56.2%)	1.76 (1.61–1.92)	< 0.001	2855 (61.7%)	1.29 (1.18–1.41)	< 0.001
Median(≥ 1-<2)	3284 (49.9%)	1.79 (1.65–1.95)	< 0.001	3066 (46.6%)	1.20 (1.10–1.30)	< 0.001	3930 (59.7%)	1.16 (1.06–1.25)	< 0.001
Low(< 1)	1462 (37.1%)	Ref		1653 (42.0%)	Ref		2293 (58.3%)	Ref	
Multivariable									
T1DM			< 0.001 ζ			0.232 ζ			0.470 ζ
High(≥ 2)	67 (59.8%)	4.77 (2.69–8.57)	< 0.001	55 (49.1%	1.24 (0.72–2.14)	0.44	69 (61.6%	1.11 (0.65–1.90)	0.71
Median(≥ 1-<2)	95 (37.8%	2.31(1.54–3.47)	< 0.001	110 (43.8%)	1.31 (0.90–1.91)	0.16	134 (53.4%)	1.20 (0.83–1.74	0.32
Low(< 1)	182 (22.1%)	Ref		301 (36.5%	Ref		396 (48.1%	Ref	

Note: Univariate model was adjusted for beta cell function categories; Multivariate model was adjusted for age, sex, beta cell function categories, current smoking status, current drinking status, BMI, HbA1c, systolic blood pressure, use of lipid lower drugs, use of oral antidiabetic drugs and insulin treatment.

ζ p for trend

Insulin resistance	High TG			Low HDL-C			High LDL-C		
	n (%)	OR (95% CI)	p	n (%)	OR (95% CI)	p	n (%)	OR (95% CI)	p
T2DM			< 0.001 ζ			< 0.001 ζ			0.004 ζ
High(≥ 2)	3024 (65.3%)	2.80 (2.49–3.15)	< 0.001	2599 (56.2%)	1.54 (1.38–1.74)	< 0.001	2855 (61.7%)	1.19 (1.06–1.33)	0.004
Median(≥ 1-<2)	3284 (49.9%)	1.71 (1.54–1.89)	< 0.001	3066 (46.6%)	1.21 (1.09–1.34)	< 0.001	3930 (59.7%)	1.10 (0.99–1.21)	0.08
Low(< 1)	1462 (37.1%)	Ref		1653 (42.0%)	Ref		2293 (58.3%)	Ref	
Note: Univariate model was adjusted for beta cell function categories; Multivariate model was adjusted for age, sex, beta cell function categories, current smoking status, current drinking status, BMI, HbA1c, systolic blood pressure, use of lipid lower drugs, use of oral antidiabetic drugs and insulin treatment.									
ζ p for trend									

Associations between HOMA2-B and risk of dyslipidemia in T1DM and T2DM

The risks of dyslipidemia (high TG, low HDL-C and high LDL-C) associated with HOMA2-B were estimated by both univariate logistic regression and multivariable logistic regression with adjustment for age, sex, insulin resistance categories, current smoking, current drinking, BMI, HbA1c, SBP, lipid lowering treatment, oral anti-diabetic treatment and insulin treatment in T1DM and T2DM (Table 3). In patients with T1DM, low HOMA2-B, i.e., < 30.0 versus ≥ 30.0, was associated with marginally increased risk of high TG in univariable analysis (OR: 1.32, 95% CI 0.98–1.79, p = 0.08) and multivariable analysis (OR: 1.42, 95% CI 0.98–2.10, p = 0.07) but not associated with low HDL-C and high LDL-C. While in patients with T2DM, HOMA2-B (< 30.0) was associated with an increased risk of high TG and high LDL-C (all p value < 0.001) in univariable regression models and remained associated with an increased risk of high TG (OR: 1.21, 95% CI 1.09–1.34, p < 0.001) and high LDL-C (OR:1.23, 95% CI 1.12–1.36, p < 0.001) in multivariable regression models (Table 3).

Table 3
Odds ratio of beta cell function for abnormal lipid profile in T1DM and T2DM

Beta cell function	High TG			Low HDL-C			High LDL-C		
	n (%)	OR (95% CI)	p	n (%)	OR (95% CI)	p	n (%)	OR (95% CI)	p
Univariable									
T1DM									
High (≥ 30)	212 (27.2%)	Ref		292 (37.4%)	Ref		391 (50.1%)	Ref	
Low(< 30)	132 (32.4%)	1.32 (0.98–1.79)	0.08	174 (42.8%)	0.92 (0.70–1.20)	0.54	208 (51.1%)	1.12 (0.86–1.46)	0.38
T2DM									
High (≥ 30)	5195 (50.9%)	Ref		2285 (46.3%)	Ref		3233 (65.5%)	Ref	
Low(< 30)	2575 (52.1%)	1.32 (1.23–1.42)	< 0.001	5033 (49.3%)	0.97 (0.91–1.04)	0.44	5845 (57.3%)	1.49 (1.38–1.60)	< 0.001
Multivariable									
T1DM									
High (≥ 30)	212 (27.2%)	Ref		292 (37.4%)	Ref		391 (50.1%)	Ref	
Low(< 30)	132 (32.4%)	1.42 (0.98–2.10)	0.07	174 (42.8%)	0.94 (0.68–1.32)	0.74	208 (51.1%)	1.08 (0.79–1.49)	0.62
T2DM									
High (≥ 30)	5195 (50.9%)	Ref		2285 (46.3%)	Ref		3233 (65.5%)	Ref	
Low(< 30)	2575 (52.1%)	1.21 (1.09–1.34)	< 0.001	5033 (49.3%)	0.93 (0.84–1.03)	0.16	5845 (57.3%)	1.23 (1.12–1.36)	< 0.001

Note: Univariate model was adjusted for insulin resistance categories; Multivariate model was adjusted for age, sex, insulin resistance categories, current smoking status, current drinking status, BMI, HbA1c, systolic blood pressure, use of lipid lower drugs, use of oral antidiabetic drugs and insulin treatment.

Discussion

In this study, we found that high IR and low BCF as estimated by the updated homeostasis model assessment had different associations with risk of dyslipidemia in patients with newly-onset T1DM and T2DM. In T1DM, high IR was associated with the risk of high TG while in T2DM, high IR was associated with increased risks of high TG, low HDL-C and high LDL-C and low BCF was associated with increased risk of high TG.

Studies in different populations reported consistent findings regarding the associations between IR and dyslipidemia. High TG, low HDL-C (p for trend = 0.052) and high LDL-C were associated with increased IR in Chinese elderly patients with newly-onset diabetes [15] and in Japanese nonobese patients with T2DM [16]. The Coronary Artery Calcification in Type 1 Diabetes Study found that high TG but not HDL-C or LDL-C was inversely associated with glucose infusion in American adult patients with T1DM [17]. The first study only included elderly patients and the latter two cohorts had an 8- and 23-year duration of diabetes, respectively. Using a large representative sample of patients with newly diagnosed diabetes, our study confirmed the above findings.

The associations of IR with high TG, low HDL-C and high LDL-C are biologically plausible. Lipid abnormalities associated with IR are very likely to be initiated by the resistance of adipocytes to insulin. Insulin-resistant fat cells lead to increased hydrolysis of TGs and release of fatty acids to the liver [18]. This can increase the synthesis of TG in the liver and stimulate the assembly and secretion of very low-density lipoprotein (VLDL), the main transporter of fasting TG and as a major contributor to the hypertriglyceridemia [19]. Decreased degradation of apolipoprotein B, the predominant surface protein of VLDL, was seen in IR states resulting from increased free fatty acids, thus causing an overproduction of VLDL [20]. An increased in TG-rich lipoproteins is often associated with an increase in small dense LDL and a decrease in HDL levels. Hypertriglyceridemia stimulates the transfer of TG-rich lipoproteins to HDL and LDL in exchange for cholesteryl esters [21], leading to increased TG content of HDL and LDL. Furthermore, the TG content is then converted to small dense LDL and small HDL. The expression of Apo-I, which can dissociate from TG-rich HDL, is decreased in patients with diabetes or with IR states, leading a reduction in HDL levels [18].

In this study, we found that low BCF associated with an increased risk of high TG and high LDL-C in T2DM. Previous studies also showed that TG/HDL-C or log(TG)/HDL-C was associated with BCF in patients with T2DM [22, 23]. However, we did not detect the association between HDL-C and BCF in T2DM. Dullaart et al also found that BCF was not significantly correlated with HDL-C in patients with well-controlled T2DM but were significantly correlated with HDL functional markers [24]. Furthermore, we observed an association of LDL-C with BCF in T2DM, suggesting a potential role of LDL-C lowering treatment in beta cell protection.

A biological link between low BCF and abnormal lipid metabolism is also plausible. Excess exposure of beta cells to free fatty acids can decrease beta cell secretory function and cause cell death [25]. Besides, insulin plays a central role in the regulation of lipid metabolism. Insulin inhibits lipolysis in the adipose tissue resulting in reduced free fatty acids into the circulation. Besides, insulin inhibits VLDL production and promotes the catabolism of TG-rich lipoproteins by activating lipoprotein lipase [26]. Thus, a relative insulin deficiency could increase VLDL production resulting in hypertriglyceridemia [27]. Insulin also stimulates the clearance of LDL by increasing LDL receptor expression and activity [28]. These effects might explain the associations between low beta cell function and an increased risk of high TG and LDL-C in those with T2DM. However, we did not observe the significant associations between BCF and risk of dyslipidemia in those with T1DM. Possible explanations could be: 1) The prevalence of dyslipidemia in T1DM is relative low. Lipid abnormalities in T1DM are more frequent in those with poor glycemic control [29], which is observed in several studies [30–32]. The lipid profile is similar in T1DM patients with good glycemic control and general population [3]. 2) An earlier study showed that insulin therapy may resolve lipid abnormalities in 24 hours in T1DM patients with diabetic ketoacidosis, by increasing TG-rich lipoprotein catabolism [33]. This finding may suggest that dyslipidemia affected by insulin insufficiency can be rapidly resolved by insulin treatment in T1DM.

Our study has clinical significances. First, we found that high IR was associated with increased risk of high TG in T1DM. Evidence also showed that anti-diabetic drugs like glucagon-like peptide-1 receptor (GLP-1R) agonists (exenatide), sodium glucose cotransporter 2 (SGLT2) inhibitors and metformin combined with insulin treatment have some beneficial effects in T1DM, such as contributing to weight loss or reducing insulin requirement [34–37]. These findings suggest that such anti-diabetic drugs combined with insulin treatment may have a potential beneficial effect on lipid metabolism by increasing insulin sensitivity and improve CVD outcomes in patients with T1DM, especially for those with obesity and insulin resistance. Additionally, it is novel and interesting to have detected significant associations of low BCF with lipid abnormalities (high TG and high LDL-C) in those with T2DM. T2DM in East Asians is characterized primarily by decreased beta-cell dysfunction [38]. Thus, our findings support early use of insulin in those T2DM patients with low BCF, which may have potential benefits for lipid metabolism and thus reduced risk of CVD in the future.

Our study has some limitations. First, our study was a cross sectional survey and causality cannot be established. It is also possible that some of the associations between low BCF and high IR with high TG, low HDL-C and high LDL-C had reverse causal relationships. Second, use of drugs, especially, lipid lowering drugs may have major confounding effects on our conclusions. Although information regarding use of these drugs was documented and we had made careful adjustment for use of those drugs, the adjustment cannot completely remove all of their confounding effects and residual confounding effects may be substantial. Third, newly-onset diagnosed patients may have beta cell function inhibition due to high glucose level, resulting in lower HOMA2-B and HOMA2-IR in those with poor glycemic control, leading to inaccurate estimation of these associations in the study.

Conclusions

In summary, in patients with newly diagnosed diabetes, IR and BCF had different associations with risk of dyslipidemia in T1DM and T2DM, supporting early use of anti-diabetes treatment that improve IR or BCF because it may have beneficial effects for lipid metabolism and therefore, reduced risk of CVD in the future.

Abbreviations

CVD: Cardiovascular disease

T1DM: Type 1 diabetes mellitus

T2DM: Type 2 diabetes mellitus

IR: Insulin resistance

BCF: Beta cell function

TG: Triglyceride

HDL-C: High-density lipoprotein cholesterol

LDL-C: Low-density lipoprotein cholesterol

OR: Odds ratios

CI: Confidence intervals

HOMA2-IR: Homeostasis model assessment of insulin resistance

HOMA2-B: Homeostasis model assessment of beta-cell function

RCS: Restricted cubic spline

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

FPG: Fasting plasma glucose

HbA1c: Hemoglobin A1c

PPG: Postprandial plasma glucose

GADA: Glutamic acid decarboxylase antibodies

IASP 2016: 2016 islet autoantibody standardization program

ADA: American Diabetes Association

SD: Standard deviation

BMI: Body mass index

VLDL: Very low-density lipoprotein

GLP-1R: Glucagon-like peptide-1 receptor

SGLT2: Sodium glucose cotransporter 2

Declarations

Ethics approval and consent to participate

The Study was approved by Ethics Committees of the Second Xiangya hospitals, Central South University in China (NO. 2014032). All individual participants provided written informed consent before data collection.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XT drafted the manuscript and performed data analysis. X Yan, XL, ZZ conceived of and designed the study. X Yan, HZ, GH, XN, HJ, XL, ZZ contributed to the data collection and conducting the study. X Yang, XL, ZZ contributed to the data interpretation and discussion. All authors reviewed and approved the manuscript in its original, revised and final form. All authors read and approved the final manuscript.

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Figures

Fig. 1

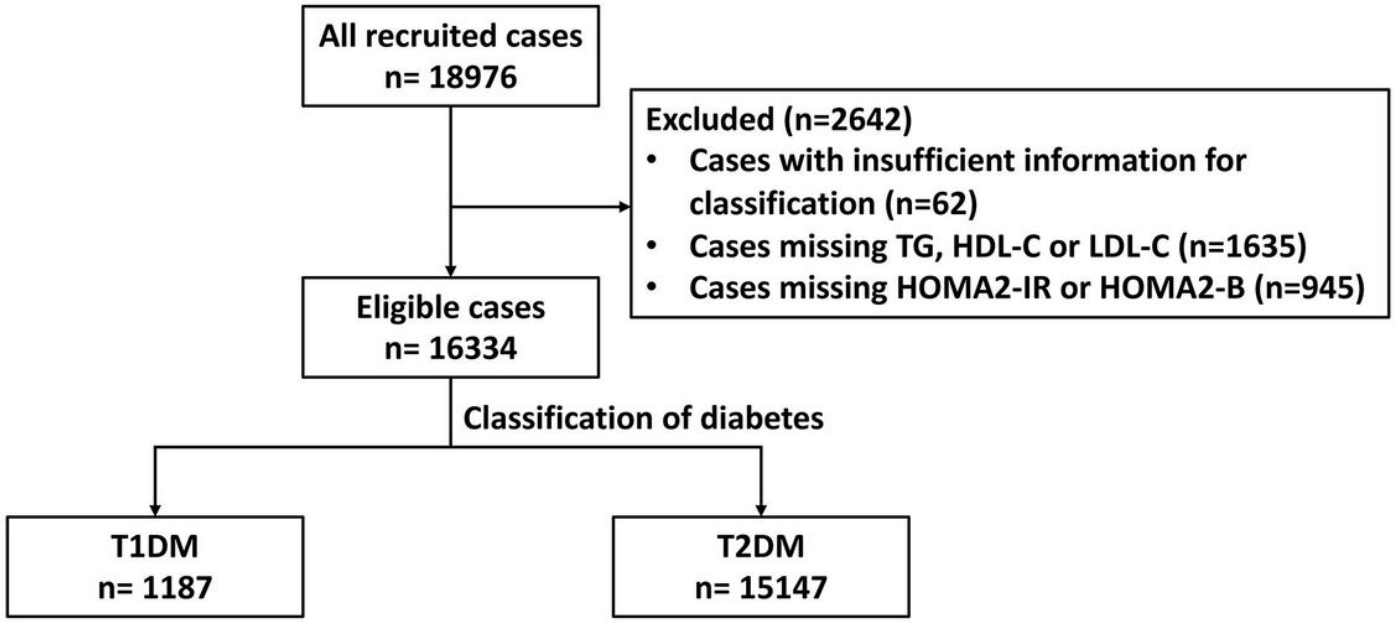

Figure 1

Flow diagram of the study patients

Fig. 2

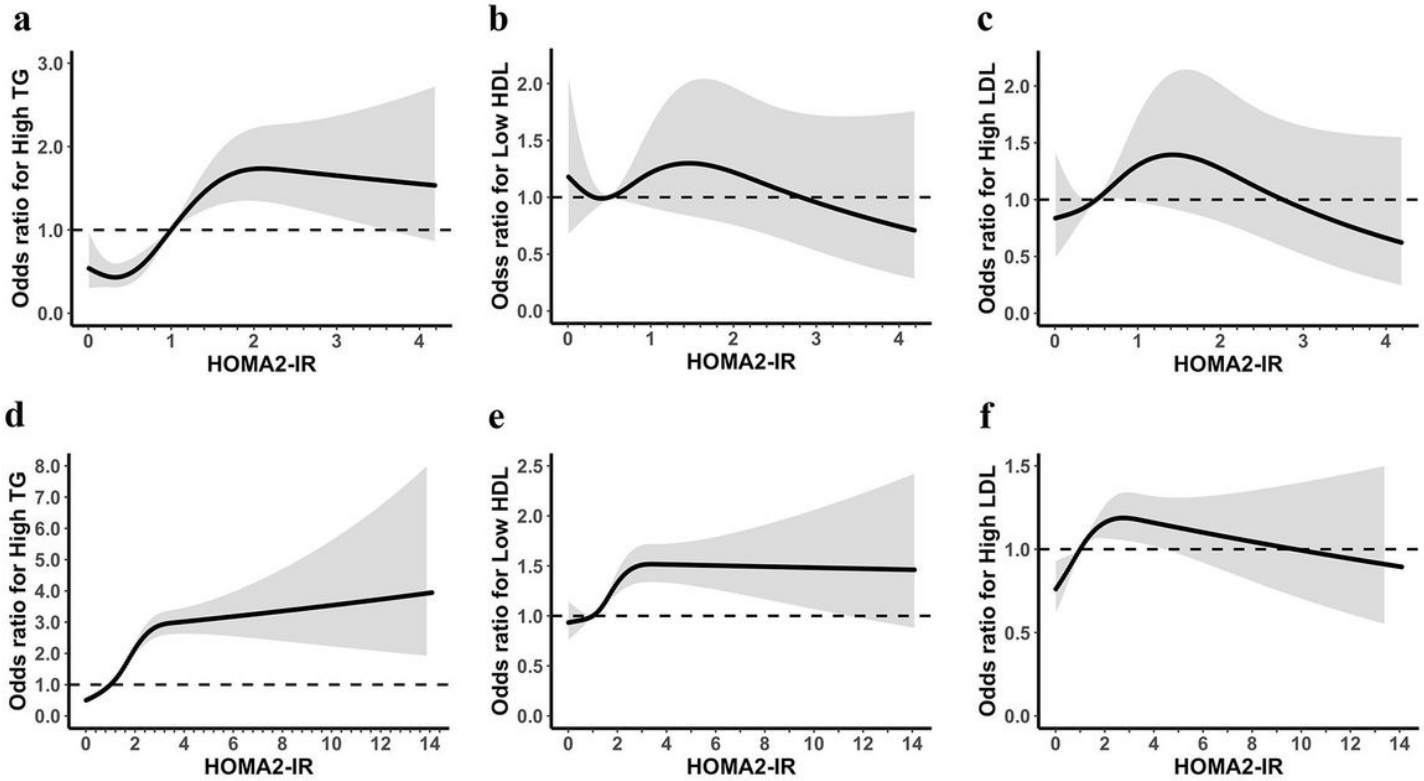

Figure 2

Associations of HOMA2-IR with risk of dyslipidemia in T1DM (a, b, c) and T2DM (d, e, f). The curves and the grey region stand for the odds ratios and 95% CIs for high TG (a, d), low HDL-C (b, e), high LDL-C (c, f). High TG was defined as TG more than 1.7 mmol/L, low HDL-C was defined as HDL-C less than 1.0 mmol/L in male and 1.3 mmol/L in female, high LDL-C was defined as LDL-C more than 2.6 mmol/L.

Fig. 3

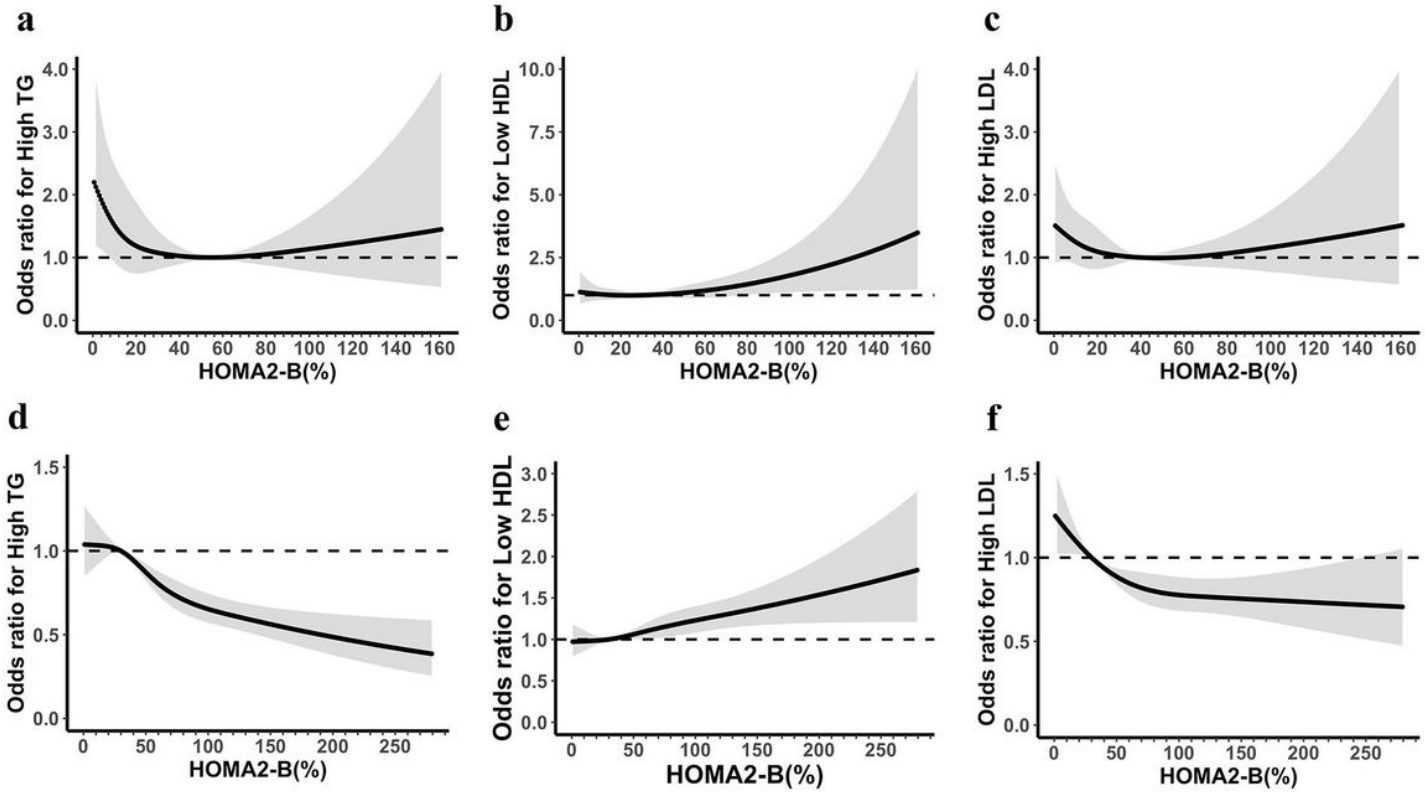

Figure 3

Associations of HOMA2-B with risk of dyslipidemia in T1DM (a, b, c) and T2DM (d, e, f). The curves and the grey region stand for the odds ratios and 95% CIs for high TG (a, d), low HDL (b, e), high LDL (c, f). High TG was defined as TG more than 1.7 mmol/L, low HDL-C was defined as HDL-C less than 1.0 mmol/L in male and 1.3 mmol/L in female, high LDL-C was defined as LDL-C more than 2.6 mmol/L.