DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2016; **32**: 572–580.
Published online 26 January 2016 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/dmrr.2770

RESEARCH ARTICLE

Utility of serum lipid ratios for predicting incident type 2 diabetes: the Isfahan Diabetes Prevention Study

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Received: 28 August 2015
Revised: 20 November 2015
Accepted: 29 November 2015

Abstract

Background In this study, we evaluate the association between triglyceride to high-density lipoprotein cholesterol (TG/HDL) ratio and total cholesterol (TC) to HDL (TC/HDL) ratio and the risks of type 2 diabetes (T2D) in an Iranian high-risk population.

Methods We analysed 7-year follow-up data ($n = 1771$) in non-diabetic first-degree relatives of consecutive patients with T2D 30–70 years old. The primary outcome was the diagnosis of T2D based on repeated oral glucose tolerance tests. We used Cox proportional hazard models to estimate hazard ratio for incident T2D across tertiles of TG/HDL and TC/HDL ratios and plotted a receiver operating characteristic (ROC) curve to assess discrimination.

Results The highest tertile of TG/HDL and TC/HDL ratios compared with the lowest tertile was not associated with T2D in age- and gender-adjusted models (HR 0.99, 95% CI: 0.88, 1.11 for TG/HDL ratio and 1.10, 95% CI: 0.97, 1.23 for TC/HDL ratio). Further adjustment for waist circumference or body mass index, fasting plasma glucose, and low-density lipoprotein cholesterol did not appreciably alter the hazard ratio compared with the age- and gender-adjusted model. The area under the ROC curve for TG/HDL ratio was 57.7% (95% CI: 54.0, 61.5) and for TC/HDL ratio was 55.1% (95% CI: 51.2, 59.0).

Conclusions TG/HDL and TC/HDL ratios were not robust predictors of T2D in high-risk individuals in Iran.

Keywords TG/HDLC ratio; lipid ratios; lipids; type 2 diabetes; first-degree relatives; incidence; risk factor

Introduction

Obesity and type 2 diabetes (T2D) is a growing health problem in Iran, and the prevalence of low high-density lipoprotein cholesterol (HDLC) level among Iranian is markedly high, and serum HDLC levels are low [1,2]. T2D prevalence in Iran is significantly higher than its neighbouring countries Pakistan (6.7% for 2007) [3] and Turkey (7.2%, for 1997–1998) [4]. On the other hand, our figures often fall below the prevalence rates observed in Arab communities

[5]. Available reports of T2D prevalence among Middle Eastern countries vary substantially, ranging from 2.8% in Israel [6] to 29% in Bahrain [7]. In a 2009 systematic review, a prevalence rate of 10.5% (95% CI: 8.6, 12.7%) in the region was recorded [8].

Although several studies demonstrated that lipid ratios, such as total cholesterol to HDLC (TC/HDLC) and triglycerides to HDLC (TG/HDLC) ratios could be better predictors of cardiovascular disease than any single measure [9], its association with T2D remains controversial. Meanwhile, only a few studies have examined lipid ratios for predicting T2D [10–12], and thus, the role of lipid ratios as a risk factor for T2D remains unsettled; reported association have been positive [10,12] or poor [11].

Recently, also several studies showed that lipid ratios were associated with insulin resistance and might be used as its surrogate [13–21], as high levels of TG and low levels of HDLC are two key metabolic abnormalities associated with insulin resistance state and might predict the development of T2D [22]. The assessment of insulin resistance is of interest because of its key role in T2D and is already present one to two decades before the diagnosis [23,24].

The high prevalence of low HDLC concentration and T2D among Iranians cannot explain only by unhealthy lifestyle behaviours. It is likely that genetic factors also influence lipids and T2D. However, the utility of lipid ratios in predicting T2D has not been explored among first-degree relatives (FDR) of patients with T2D. The FDR of patients with T2D that have a genetic basis are vulnerable to T2D [25] and might be more appropriate for testing this hypothesis.

The objective of this ongoing longitudinal study, therefore, was to evaluate the association between several lipid measures (including TC/HDLC and TG/HDLC ratios) and incidence of T2D in an Iranian high-risk population. We hypothesized that the TG/HDLC and TC/HDLC ratios would predict incidence of T2D in FDR of patients with T2D.

Subjects and methods

Data collection

This study was conducted within the framework of the Isfahan Diabetes Prevention Study. The Isfahan Diabetes Prevention Study, initiated in 2003, is an ongoing cohort in central Iran to assess the various potential risk factors for diabetes in subjects with family history of T2D (one of the main risk factors for diabetes). The recruitment methods and examination procedures of the Isfahan Diabetes Prevention Study have been previously described [26]. Our study sample at baseline comprised 3483 (919 men and 2564 women) FDR of consecutive patients with T2D. All patients were attendees at clinics at Isfahan Endocrine and Metabolism Research Center, which is affiliated to Isfahan University of Medical Sciences, Iran. The study was conducted between the years 2003 and 2005. All participants were from Isfahan city and adjoining areas. They completed laboratory tests including a standard 75 g 2-h oral glucose tolerance test (OGTT), fasting serum lipid profiles, and a questionnaire on their health status and on various potential risk factors for diabetes. Participants received follow-up tests according to Standard of Medical Care in Diabetes [27] to update information on demographic, anthropometric, and lifestyle factors and on newly diagnosed diabetes. Accordingly, if OGTT at baseline was normal, repeat testing was carried out at least at 3-year intervals. Otherwise, repeat testing was usually carried out annually.

Ethics statement

The Iranian government's ethical guidelines regarding epidemiological studies in agreement with the current version of the Declaration of Helsinki were followed, and Isfahan University of Medical Sciences ethical committee approved this study, and an informed consent form was signed by each participant.

Follow-up and ascertainment of T2D

Among 3483 persons who participated at baseline, 329 subjects were excluded because of diagnosis of T2D at baseline and 1285 did not attend any follow-up examination and 98 with missing data for HDLC at baseline, leaving 1771 participants with a mean age 43.0 (6.5) (range 30–70) years for this analysis, all of whom had at least one subsequent review during a mean [standard deviation (SD)] follow-up period of 7.3 (2.2) (range 1–10) years. Pregnant women were excluded. The most baseline characteristics of individuals who did not return for follow-up visit, such as age, height, weight, body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), low-density lipoprotein cholesterol (LDLC), TC, TG, systolic blood pressure (BP), and obesity were similar to those attended in the follow-up visits. However, those who did not return for follow-up compared with respondents had slightly lower fasting plasma glucose (FPG) (94.7 *vs.* 95.6 mg/dL, $p < 0.05$), plasma glucose (PG) at 30 min (139.5 *vs.* 144.2 mg/dL, $p < 0.001$), 60 min (140.8 *vs.* 149.8 mg/dL, $p < 0.001$), and 120 min (110.6 *vs.* 119.5 mg/dL, $p < 0.001$), levels of glycosylated hemoglobin (HbA_{1c}) (5.0% *vs.* 5.1, $p < 0.05$), diastolic BP (73.4 *vs.* 75.7 mmHg, $p < 0.001$), and higher HDLC (46.7 *vs.* 45.0 mg/dL, $p < 0.001$).

Clinical and laboratory measurements

Information on age, gender, body size, HbA_{1c}, TC, LDLC, HDLC, TG, BP, and family and personal medical history was collected at baseline and through follow-ups. The same methodology was used for baseline and follow-up studies. The participants included siblings and children of patients with T2D. Participants reported to clinics in the morning after an overnight fast. They were asked to abstain from vigorous exercise in the evening and in the morning of their visit. Smokers were

DOI: 10.1002/dmrr

encouraged to abstain from smoking in the morning of the investigations. First, on arrival at the clinic, the information provided by the participants in the questionnaire on family history was verified. Then, with the subjects in light clothing and without shoes, height, weight, WC, and HC were measured using standard apparatus. Weight was measured to the nearest 0.1 kg on a calibrated beam scale. Height, WC, and HC were measured to the nearest 0.5 cm with a measuring tape. The waist was measured midway between the lower rib margin and the iliac crest at the end of gentle expiration in the standing position. HC was measured over the greater trochanters directly over the underwear. The BMI was calculated as the weight in kilograms divided by square of the height in meters. Resting BP was measured at each examination by physician with the participants in a sitting position after being seated for 10 min with a mercury column sphygmomanometer and appropriately sized cuffs, using standard techniques. A blood sample was drawn between 7.00 and 9.00 AM. FPG was measured using an enzymatic colorimetric method with the glucose oxidase. Participants with FPG ≥200 mg/dL or pharmacological treatment were considered as persons with diabetes. If FPG was ≥126 and <200 mg/dL, a second FPG was measured on another day. If the second FPG was also ≥126 mg/dL, participants were considered as persons with diabetes [28]. Those with FPG <126 mg/dL underwent a standard OGTT (75 g glucose 2 h) at baseline and the follow-up visits. Venous blood was sampled 0, 30, 60, and 120 min after oral glucose administration. Plasma samples were centrifuged and analysed the same day.

HbA_{1c} (measured by ion exchange chromatography), TC, TG, HDLC, and LDLC were recorded. The LDLC levels were calculated with the Friedewald equation [29] provided that total TG did not exceed 400 mg/dL. Non-HDLC was calculated by subtracting HDLC from TC. All blood sampling procedures were performed in the central laboratory of the Isfahan Endocrine and Metabolism Research Center using enzyme-linked method. The lipid variables or ratios evaluated in the present study include TC, LDLC, HDLC, non-HDLC, TG, TG/HDLC ratio, and TC/HDLC ratio.

To convert TG to millimoles per liter, multiply by 0.0113; HDLC, LDLC, and TC to millimoles per liter, multiply by 0.0259; and glucose to millimoles per liter, multiply by 0.0555.

Analysis

Incidence was expressed as the number of cases of T2D per 1000 person-years of follow-up beginning on the date of completion of the baseline examination in 2003 to 2005 and continuing until the occurrence of T2D, the date of the last completed follow-up, death, or end of follow-up on 21 March 2014, whichever came first.

Statistical methods included the Student's *t*-test or Mann–Whitney *U* test, one-way analysis of variance (ANOVA) with Scheffe's method as the *post hoc* analysis or the Kruskal–Wallis test with the Dunn procedure for continuous variables, the chi squared test, and Cox proportional hazard models. To test the significance of TG/HDLC and TC/HDLC ratios as a predictor of incidence of T2D, the incidence of T2D was calculated according to the tertile of TC/HDLC and TG/HDLC ratios and compared the risk of developing T2D in each tertile with the lowest TC/HDLC and TG/HDLC ratio category (reference group). Univariate and multivariate Cox's proportional hazard models were fitted to investigate the relations of the various lipid measures to T2D incidence, adjusting for age, gender, systolic BP, FPG, HbA_{1c}, and BMI or WC (all defined at the baseline examination) using the SPSS version 18 for Windows (SPSS Inc., Chicago, IL, USA). Pearson correlation coefficients were estimated for the interrelation between the various lipid measurements after holding the effect of age and gender constant. The ability of reversed HDLC, TG, TC, TG/HDLC, and TC/HDLC ratios to predict incidence T2D was examined with receiver operating characteristic (ROC) curves and their respective areas under the curve, in which sensitivity was plotted as a function of 1 − specificity. The area under the ROC curve is a global summary statistic of the discriminative value of a model, describing the probability that an individual developing than an individual not developing T2D would be correctly identified based on the level of the lipid measures in a randomly chosen subject pair (one with and one without T2D). The area under the ROC curve was used as an index of global test performance of lipid measures for identification of T2D across the entire range of values, with an area under the curve of 0.5 indicating no discrimination ability. Conventionally, an area under the curve of 0.90 or more is considered excellent, values between 0.80 and 0.90 regarded as good, between 0.70 and 0.80 indicate of fair test performance, and values between 0.50 and 0.70 viewed as poor [30]. Areas under the ROC curves were compared by the algorithm developed by DeLong et al. [31]. Age-adjusted means were calculated and compared using general linear models. We did not conduct gender-specific analyses because there were too few events in some subgroups to calculate stable risk estimates. All tests for statistical significance were two-tailed, and all were carried out assuming a type I error probability of <0.05.

Results

Characteristics

A total of 261 (14.8%) (67 men and 194 women) incident cases of T2D occurred during 12 771 (3199 men and 9572 women) person-years of follow-up. Baseline

DOI: 10.1002/dmrr

characteristics of the 261 (14.8%) participants who did and 1510 (85.2%) who did not progress to T2D are shown in Table 1. As expected, participants who progressed to T2D were older and had higher age-adjusted mean weight, BMI, WC, WHR, HC, follow-up duration, FPG, and PG at 30, 60, and 120 min, higher HbA_{1c}, TG, TC, non-HDLC, TC/HDLC, and TG/HDLC ratios at baseline, and a higher proportion of obesity.

The mean (SD) age was 44.4 (6.7) years for those progress to T2D and 42.7 (6.3) years for those who did not progress to T2D. The mean (SD) TC/HDLC and TG/HDLC ratios were 4.8 (1.5) and 4.9 (4.2) for those progress to T2D and 4.5 (1.3) and 4.0 (2.9) for those who did not progress to T2D, respectively.

The age- and gender-adjusted correlations among the lipid variables are shown in Table 2. As expected, there is a reciprocal relationship between HDLC and TG ($r = -0.223$), and each of these lipids, except TC, was strongly related to TG/HDLC ratio. The TC was moderately correlated with the TG ($r = 0.272$) and with the TC/HDLC ratio ($r = 0.400$). As expected, the TC/HDLC ratio was also correlated with the TG/HDLC ratio ($r = 0.618$)

The baseline characteristics of the study participants by TC/HDLC and TG/HDLC ratio tertiles are shown in Table 3. In comparisons of variables at baseline, all variables were more likely to increase, while HDLC and women proportion were more likely to decrease across all three subject groups.

Incidence of diabetes

The overall incidence of subsequent diabetes was 20.4 (95% CI: 18.0, 22.9) per 1000 person-years. Incidence rates were similar in women (20.3, 95% CI: 17.5, 23.2 per 1000 person-years) and men (20.9, 95% CI: 16.2, 26.4).

The incidence of T2D was 16.8 per 1000 person-years (95% CI 13.0, 20.5) for participants in the lowest tertile of TC/HDLC and 26.2 per 1000 person-years (95% CI 21.3, 31.2) for the highest tertile. Compared with participants in the lowest tertile, the risk of T2D was similar to

Table 1. Age, age-adjusted mean (SE), and proportion characteristics[1] of selected baseline characteristics in 261 first-degree relatives of patients with type 2 diabetes who did and 1510 who did not develop type 2 diabetes

	Progressed to T2D	Did not progress to T2D
Variables	Mean (SE)	Mean (SE)
Age (year)	44.4 (0.39)	42.7 (0.16)***
Height (cm)	159.3 (0.50)	159.9 (0.21)
Weight (kg)	76.8 (0.72)	73.3 (0.30)***
Body mass index (kg/m^2)	30.3 (0.25)	28.7 (0.10)***
Waist circumference (cm)	92.1 (0.57)	88.7 (0.24)***
Waist-to-hip ratio	0.84 (0.004)	0.83 (0.002)*
Hip circumferences (cm)	110.0 (0.53)	107.0 (0.22)***
Follow-up duration (year)	7.8 (0.13)	7.2 (0.05)***
Systolic BP (mmHg)	117.4 (0.98)	115.5 (0.40)
Diastolic BP (mmHg)	77.0 (0.72)	75.5 (0.30)
Fasting plasma glucose (mg/dL)	104.4 (0.68)	94.1 (0.28)***
Plasma glucose 30 min (mg/dL)	163.9 (1.87)	140.7 (0.78)***
Plasma glucose 60 min (mg/dL)	186.5 (2.41)	143.2 (1.01)***
Plasma glucose 120 min (mg/dL)	146.7 (1.89)	114.6 (0.79)***
HbA_{1c} (%)	5.4 (0.05)	5.0 (0.02)***
HbA_{1c} (mmol/mol)	36 (0.33)	31 (.12)***
Triglyceride (mg/dL)	194.5 (6.04)	161.3 (2.52)***
Cholesterol (mg/dL)	201.0 (2.43)	195.7 (1.01)*
HDL cholesterol (mg/dL)	44.0 (0.73)	45.2 (0.30)
LDL cholesterol (mg/dL)	120.3 (2.20)	119.3 (0.89)
Non-HDLC (mg/dL)	156.3 2.34)	150.7 (0.1.00)*
TC/HDLC (mg/dL)	4.8 (0.08)	4.6 (0.03)**
TG/HDLC (mg/dL)	4.9 (0.20)	4.0 (0.08)***
	%	%
Women	74.5	73.8
Normal weight (BMI <25 kg/m^2)	9.4	17.1***
Overweight (BMI 25–29.9 kg/m^2)	43.5	48.3***
Obese (BMI ≥30 kg/m^2)	47.1	34.6***

HDL, high-density lipoprotein; LDL, low-density lipoprotein; BP, blood pressure; TC/HDL, cholesterol-to-high-density lipoprotein cholesterol; TG/HDL, triglyceride-to-high-density lipoprotein cholesterol; Non-HDLC, non-high-density lipoprotein cholesterol; T2D, type 2 diabetes.
[1]Age-adjusted means were calculated using general linear models. Differences in the mean or percentage values of variables between T2D and no T2D.
*$p < 0.05$,
**$p < 0.01$,
***$p < 0.001$.

DOI: 10.1002/dmrr

Table 2. Age- and gender-adjusted correlation coefficients among lipid parameters

	TG	HDLC	Cholesterol	LDLC	Non-HDLC	TG/HDLC	TC/HDLC
TG	1.00	−0.223*	0.272*	−0.033	0.356*	0.825*	0.416*
HDLC		1.00	0.317*	0.113*	0.020	−0.555*	−0.676*
Cholesterol			1.00	0.908*	0.954*	0.017	0.400*
LDLC				1.00	0.922*	−0.136*	0.506*
Non-HDLC					1.00	0.193*	0.634*
TG/HDLC						1.00	0.618*

HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TG, triglyceride; Non-HDLC, non-high-density lipoprotein cholesterol.
*$p < 0.001$.

those in the second tertile at baseline (hazard ratio (HR) 1.00; 95% CI: 0.89, 1.12) and those in the third tertile (HR 1.10; 95% CI: 0.97, 1.23) in age- and gender-adjusted models. Controlling for age, gender, WC or BMI, LDLC, and FPG did not appreciably alter the HR compared with the age- and gender-adjusted model. The results were almost similar for TG/HDLC ratio (Table 4). The directions and the strengths of the relationships were similar in analyses in which we adjusted for BMI instead of WC.

The ROC curves for the incidence of T2D for reversed HDLC, TC, TG, non-HDLC, TG/HDLC, and TC/HDLC ratios are shown in Figure 1. The areas under the ROC curves for predicting T2D from the largest to the least area were 0.580 (95% CI: 0.542, 0.618, $p < 0.001$) for TG, 0.577 (95% CI: 0.540, 0.615, $p < 0.05$) for TG/HDLC ratio, 0.551 (95% CI: 0.512, 0.590, $p < 0.05$) for TC/HDLC ratio, 0.542 (95% CI: 0.504, 0.581, $p < 0.05$) for non-HDLC, 0.537 (95% CI: 0.499, 0.5576, not significant) for TC, and 0.533 (95% CI: 0.495, 0.571, not significant) for HDLC. HDLC and TC had area smaller than that of other lipid profiles. The discriminatory power of TG, TG/HDLC and TC/HDLC ratios, and non-HDLC to identified individuals with T2D was almost the same. Areas under the ROC curves were compared with TC/HDLC and TG/HDLC ratios by the algorithm developed by DeLong et al. [31]). According to area under the ROC curves, lipid measures were shown to be poor marker for identifying individuals with T2D.

Discussion

Current study showed that performance of TG/HDLC and TC/HDLC ratios for predicting T2D in a cohort of high-risk individuals in Iran was poor as reflected by the area under the ROC curve of 57.7 and 55.1% respectively. With regard to clinical applicability, this result suggests that lipid measures should be recognized as poor marker for identifying individuals with T2D among non-diabetic FDR of patients with T2D. The TC/HDLC ratio was almost as powerful predictor of T2D risk as the TG/HDLC ratio and other lipid measures. This was unexpected given that FDR of patients with T2D have a high propensity to develop T2D at a younger age and probably at a lower BMI and WC. Only a few cohort studies [10–12] have assessed the risk of T2D based on the lipid ratios, and some other studies assessed lipid ratios as surrogate for insulin resistance [13–21]. The ability of the TG/HDLC and TC/HDLC ratios to predict the incidence of T2D in our study confirms prior reports that have noted that the combination of high TG or TC and low HDLC is a poor predictor for T2D. Hadaegh et al. [10] in 5201 non-diabetic individuals followed for median 6.4 years showed that TC/HDLC and TG/HDLC ratios were similarly predictors of T2D in men, whereas among women, TG/HDLC ratio highlighted higher risk than did TC/HDLC ratio, although there was no difference in discriminatory power. The performance of TG/HDLC and TC/HDLC ratios for predicting T2D was poor as reflected by the area under the ROC curve of 59.0 and 60.0% for men and 65 and 69% for women respectively. He et al. [11] in 687 non-diabetic individuals followed for 15 years in an urban community in China also showed that the T2D discriminatory power of TG/HDLC was poor. Vega et al. [12] in 22 215 men followed for 14.7 years showed that incidence of T2D was significantly higher in men with TG/HDL ratio greater than 3.5 than does less than 3.5. They did not present the ROC analysis. Previous observations also showed that the TG/HDLC ratio is an index of insulin resistance as high levels of TG and low levels of HDLC are two key metabolic abnormalities associated with insulin resistance state [13,16–21,32].

As judged from the respective area under the ROC curve, the relationship of incidence diabetes with TG/HDLC ratio was almost similar to that with TC/HDLC ratio and TG. As a consequence, TG/HDLC ratio appeared to be not a better predictor of T2D than TG in our study population. TG had been also advocated in literature as T2D prediction tools [33,34]. Beside lower HDLC and PG, obesity, hypertension, and higher initial TGs are relevant components of the early pathophysiology of T2D [35,36]. Therefore, it is necessary to take account of these metabolic syndrome components to determine

DOI: 10.1002/dmrr

Table 3. Age and age-adjusted mean (SE), and proportion characteristics[1] of first-degree relatives of patients with type 2 diabetes by triglyceride to high-density lipoprotein cholesterol (TG/HDLC) and total cholesterol/HDLC (TC/HDLC) tertile, the Isfahan Diabetes Prevention Study

		Tertile of TG/HDLC ratio		
Characteristic	Total	First (<2.54)	Second (2.54–4.20)	Third (>4.20)
Participants no. (%)	1766 (100)	588 (33.3)	588 (33.3)	590 (33.4)
Age (year.)	43.0 (0.15)	42.2 (0.26)	43.3 (0.26)	43.4 (0.26)**
Height (cm)	159.8 (0.20)	158.6 (0.34)	159.5 (0.34)	161.4 (0.34)***
Weight (kg)	73.8 (0.28)	71.1 (0.49)	73.9 (0.49)	76.6 (0.49)***
Waist circumference (cm)	89.2 (0.23)	86.2 (0.39)	89.4 (0.38)	92.0 (0.38)***
Hip circumference (cm)	107.5 (0.21)	106.6 (0.37)	107.8 (0.37)	108.0 (0.37)*
Waist-to-hip ratio	0.83 (0.002)	0.81 (0.003)	0.83 (0.003)	0.85 (0.003)***
Body mass index (kg/m^2)	28.9 (0.10)	28.3 (0.17)	29.1 (0.17)	29.4 (0.17)***
FPG (mg/dL)	95.7 (0.29)	95.0 (0.49)	95.7 (0.49)	96.4 (0.49)
PG 30 min (mg/dL)	144.2 (0.77)	140.9 (1.32)	144.4 (1.31)	147.2 (1.32)**
PG 60 min (mg/dL)	149.9 (1.04)	142.4 (1.76)	151.2 (1.77)	156.2 (1.76)***
PG 120 min (mg/dL)	119.7 (0.80)	116.5 (1.38)	120.2 (1.38)	122.3 (1.38)*
HbA_{1c} (%)	5.1 (0.02)	5.0 (0.04)	5.1 (0.04)	5.1 (0.04)
HbA_{1c} (mmol/mol)	32 (0.12)	31 (0.25)	32 (0.25)	32 (0.25)
Cholesterol (mg/dL)	196.7 (0.96)	190.5 (1.63)	197.7 (1.61)	202.0 (1.62)***
LDL (mg/dL)	119.4 (0.84)	118.3 (1.42)	123.9 (1.41)	115.8 (1.49)***
HDL (mg/dL)	45.0 (0.28)	53.4 (0.40)	44.5 (0.40)	37.3 (0.40)***
Triglyceride (mg/dL)	165.8 (2.37)	94.5 (2.98)	145.7 (2.97)	256.5 (2.96)***
Non-HDLC	151.7 (0.92)	137.1 (1.49)	153.1 (1.48)	164.7 (1.48)***
Cholesterol/HDLC (mg/dL)	4.6 (0.03)	3.7 (0.04)	4.5 (0.04)	5.6 (0.04)***
Triglyceride/HDLC (mg/dL)	4.1 (0.08)	1.8 (0.09)	3.3 (0.09)	7.2 (0.09)***
Systolic BP (mmHg)	115.6 (0.39)	113.5 (0.64)	115.7 (0.64)	118.2 (0.64)***
Diastolic BP (mmHg)	75.7 (0.29)	73.5 (0.49)	75.7 (0.49)	77.9 (0.48)***
Women, no. (%)	1307 (74.1)	485 (82.5)	450 (76.7)	371 (63.1)***
Overweight (BMI ≥25)	1468 (84.2)	452 (53.1)	491 (84.8)	525 (89.9)***
Abdominal obesity, no. (%)	767 (44.2)	181 (23.6)	256 (33.4}	330 (43.0)***
		Tertile of TC/HDLC ratio		
		First (<3.95)	Second (3.95–4.97)	Third (>4.97)
Participants no. (%)	1771 (100)	590 (33.3)	590 (33.3)	591 (33.4)
Age (year)	43.0 (0.15)	42.0 (0.26)	43.0 (0.26)	43.9 (0.26)***
Height (cm)	159.8 (0.20)	158.6 (0.34)	159.6 (0.34)	161.2 (0.34)***
Weight (kg)	73.9 (0.28)	71.2 (0.49)	73.9 (0.49)	76.5 (0.49)***
Waist circumference (cm)	89.2 (0.23)	86.7 (0.39)	89.1 (0.39)	91.8 (0.39)***
Hip circumference (cm)	107.5 (0.21)	106.9 (0.37)	107.7 (0.36)	107.9 (0.37)
Waist-to-hip ratio	0.83 (0.002)	0.81 (0.003)	0.83 (0.003)	0.85 (0.003)***
Body mass index (kg/m^2)	28.9 (0.10)	28.3 (0.17)	29.0 (0.17)	29.4 (0.17)***
FPG (mg/dL)	95.6 (0.29)	94.6 (0.49)	95.2 (0.49)	97.2 (0.49)***
PG 30 min (mg/dL)	144.1 (0.77)	141.8 (1.31)	144.4 (1.31)	145.9 (1.32)
PG 60 min (mg/dL)	149.7 (1.04)	144.2 (1.77)	150.1 (1.76)	155.0 (1.78)***
PG 120 min (mg/dL)	119.6 (0.80)	117.7 (1.39)	119.3 (1.38)	121.7 (1.39)
HbA_{1c} (%)	5.1 (0.02)	5.1 (0.04)	5.0 (0.04)	5.2 (0.04)*
HbA_{1c} (mmol/mol)	32 (0.12)	32 (0.25)	31 (0.25)	33 (0.25)*
Cholesterol (mg/dL)	196.5 (0.96)	177.9 (1.52)	197.8 (1.51)	213.8 (1.51)***
LDL (mg/dL)	119.4 (0.84)	99.7 (1.28)	122.7 (1.28)	136.9 (1.31)***
HDL (mg/dL)	45.0 (0.28)	54.3 (0.38)	44.6 (0.38)	36.1 (0.38)***
Triglyceride (mg/dL)	165.8 (2.37)	122.4 (3.79)	158.6 (3.76)	216.0 (3.77)***
Non-HDLC	151.5 (0.91)	123.6 (1.26)	153.2 (1.26)	177.7 (1.26)***
Cholesterol/HDLC (mg/dL)	4.6 (0.03)	3.3 (0.03)	4.4 (0.03)	6.0 (0.03)***
Triglyceride/HDLC (mg/dL)	4.1 (0.08)	2.3 (0.11)	3.6 (0.11)	6.3 (0.11)***
Systolic BP (mmHg)	115.6 (0.39)	113.4 (0.64)	115.8 (0.64)	117.7 (0.64)***
Diastolic BP (mmHg)	75.7 (0.29)	74.1 (0.48)	75.3 (0.48)	77.7 (0.49)***
Women, no. (%)	1312 (74.1)	484 (82.2)	455 (77.1)	373 (63.1)***
Overweight (BMI ≥25)	1475 (84.3)	468 (80.3)	484 (83.3)	523 (89.4)***
Abdominal obesity, no. (%)	767 (44.2)	186 (24.3)	245 (31.9)	336 (43.8)***

Data are expressed as mean (SE) or number (%).
FPG, fasting plasma glucose; PG, plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BP, blood pressure; Non-HDLC, non-high-density lipoprotein cholesterol.
[1]Age-adjusted means were calculated using general linear models.
*$p < 0.001$,
**$p < 0.01$,
***$p < 0.05$ comparison across all three groups.

DOI: 10.1002/dmrr

Table 4. Incidence rates and hazard ratio (HR)[1] of type 2 diabetes by triglyceride (TG) to high-density lipoprotein cholesterol (HDLC) ratio tertile, the Isfahan Diabetes Prevention Study

	Tertiles of TG/HDLC ratio		
	First (<2.54)	Second (2.54–4.20)	Third (>4.20)
Number of cases (%)	69 (26.4)	80 (30.7)	112 (42.9)
Person-year	4266	4252	4198
Incidence/1000 person-year (95% CI)	16.2 (12.4, 20.0)	18.8 (14.7, 22.9)	26.7 (21.8, 31.6)
Hazard ratio (95% CI)			
Unadjusted	1.00	0.98 (0.87, 1.09)	1.03 (0.92, 1.16)
Gender adjusted	1.00	0.97 (0.87, 1.09)	1.02 (0.90, 1.14)
Age and gender adjusted	1.00	0.95 (0.85, 1.07)	0.99 (0.88, 1.11)
Age, gender, and WC adjusted	1.00	0.94 (0.84, 1.06)	0.98 (0.87, 1.11)
Age, gender, triglyceride, and WC adjusted	1.00	0.92 (0.81, 1.04)	0.92 (0.78, 1.07)
Age, gender, triglyceride, WC, and LDLC adjusted	1.00	0.89 (0.78, 1.01)	0.88 (0.72, 1.07)
Age, gender, triglyceride, WC, and FPG adjusted	1.00	0.88 (0.78, 1.01)	0.90 (0.74, 1.09)
	Tertiles of TC/HDLC ratio		
	First (<3.95)	Second (3.95–4.97)	Third (>4.97)
Number of cases (%)	74 (28.4)	81 (31.0)	106 (40.6)
Person-year	4417	4312	4042
Incidence/1000 person-year (95% CI)	16.8 (13.0, 20.5)	18.8 (14.7, 22.8)	26.2 (21.3, 31.2)
Hazard ratio (95% CI)			
Unadjusted	1.00	1.02 (0.91, 1.14)	1.14 (1.02, 1.28)*
Gender adjusted	1.00	1.01 (0.90, 1.14)	1.13 (1.00, 1.27)*
Age and gender adjusted	1.00	1.00 (0.89, 1.12)	1.10 (0.97, 1.23)
Age, gender, and WC adjusted	1.00	0.99 (0.88, 1.11)	1.10 (0.98, 1.24)
Age, gender, triglyceride, and WC adjusted	1.00	0.98 (0.87, 1.10)	1.09 (0.96, 1.23)
Age, gender, triglyceride, WC, and LDLC adjusted	1.00	0.90 (0.80, 1.03)	0.92 (0.79, 1.08)
Age, gender, triglyceride, WC, LDLC, and FPG adjusted	1.00	0.92 (0.81, 1.05)	0.95 (0.81, 1.11)

CI, confidence interval; WC, waist circumference; BMI, body mass index; TG, triglyceride; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; FPG, fasting plasma glucose.
[1]Hazard ratio (with 95% CI) calculated by Cox proportional hazard model.
$^{**}p < 0.01$,
$^{*}p < 0.05$.

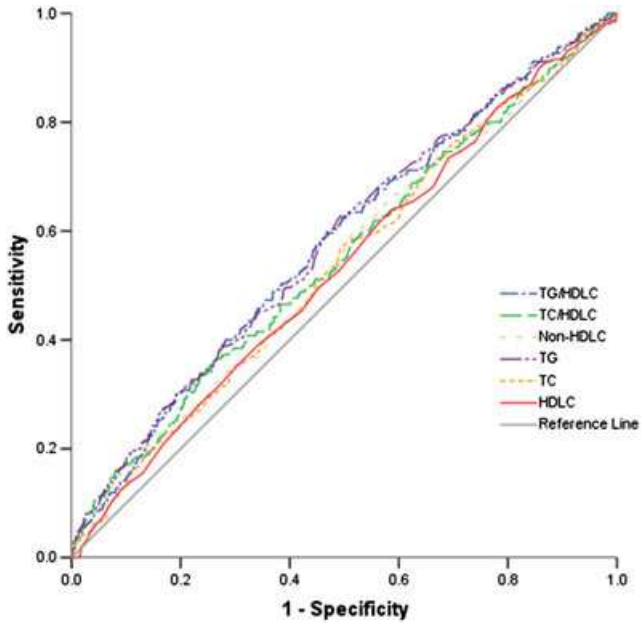

Figure 1. Receiver operating characteristic (ROC) curves for evaluating the usefulness of total cholesterol (TC), reversed high-density lipoprotein cholesterol (HDLC), triglyceride (TG), non-HDLC, total cholesterol to high-density lipoprotein cholesterol (TC/HDLC) ratio, and triglyceride to high-density lipoprotein cholesterol (TG/HDLC) ratio to identify type 2 diabetes in first-degree relatives of patients with type 2 diabetes. The estimates of the area under the ROC curves and their 95% confidence intervals are shown

DOI: 10.1002/dmrr

the strength of the relationships of lipid ratios with incidence T2D.

Our study has several strengths and limitations. The strengths include the use of a sample consisting of men and women, performance of standard OGTT, information on potential determinants of T2D, and using the direct measurements of the anthropometric indices rather than self-reported data. At follow-up, non-attendees in the entire population did not differ from attendees according to major risk factors for progression to T2D, although a difference too small to explain the high progression rate to T2D in our study was seen in the mean levels of PG. Our database is one of the few that followed FDR of patients with T2D, thereby enabling us to simultaneously control the genetic factors that may predict T2D. Our study is also the only one in which TG/HDLC ratio was measured for evaluation of the risk of developing T2D over a 7-year period among a FDR of patients with T2D population. Our study was limited to a cohort of individuals who are at increased risk of developing T2D, because they had a FDR with the patients with T2D; thus, the selection bias may lead to an overestimation of associations. In terms of our definition of incidence T2D, some selection bias may be present as participants who attend for screening may have been more likely to be tested and consequently diagnosed as having T2D. Thus, participants with T2D who had lower risk may have been missed through lack of testing. We did not conduct gender-specific analyses because there were too few events in some subgroups to calculate stable risk estimates, and we used gender as an adjustment factor in all analyses. Of note, McLaughlin et al. [17] did not detect any interaction between gender and the ability of the TG/HDLC ratio to predict insulin resistance. We did not evaluate LDLC because it was calculated, rather than measured, albeit it has not been reported to have a strong correlation with insulin resistance in the literature [37]. The current findings were drawn from a study population with FDR of patients with T2D and a high prevalence of low HDLC, and therefore, the results might not be generalized to all populations. Finally, we had no data on diet that might have influenced the extent to which TG/HDLC and TC/HDL ratios associated with T2D. However, it is necessary to validate the association of lipid ratios and T2D in other populations. However, this study is meaningful as a first study to clarify the relationship between lipid ratios and incident T2D among an Iranian population of FDR of patients with T2D.

In conclusion, these data provides further evidence that lipid ratios such as TG/HDLC and TC/HDLC ratios are not robust predictors for future development of T2D in non-diabetic high-risk individuals in Iran. This study suggests that although lipid ratios could exert a beneficial metabolic effect for prevention of T2D, it was not better than single TGs at discriminating diabetes risk in this high-risk population, known to have a high prevalence of prediabetes and T2D.

Acknowledgements

We are grateful to M. Abyar for technical computer assistance. This study could not have been conducted without the contributions of the relatives of patients with type 2 diabetes who consented to participate. This study was supported partially by a grant from the Isfahan University of Medical Sciences, Iran. This research was performed as a part of the academic activity of the university.

Authors contributions

Janghorbani M conceived and designed the study, analysed and interpreted the data, and drafted the manuscript; Amini M recruited samples and contributed to the discussion and revision of the manuscript and obtained funding for the Isfahan Diabetes Prevention Study. All of the authors approved the final version submitted for publication.

Conflicts of interest

The authors have no conflicts of interest.

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