

Association of serum lipoprotein ratios with insulin resistance in type 2 diabetes mellitus

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Background: The fasting serum total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL-C) and low density lipoprotein (LDL-C) levels are used to calculate following lipid ratios: TC/HDL-C, TG/HDL-C, and LDL-C/HDL-C. Cholesterol retention fraction (CRF), non-HDL-C, LDL-C, TG and waist circumference (WC) one considered as markers for the identification of individuals with an increased risk for cardiovascular diseases (CVD). These individuals frequently show insulin resistance as well. We analyzed the association of lipoprotein ratios with the homeostasis model assessment of insulin resistance (HOMA-IR).

Methods: Type 2 diabetes mellitus (T2D) patients (92) and 40 age match healthy controls were randomized from the Tapho Primary Health Care Unit and the area in the same district. The HOMA-IR was used to calculate for insulin resistance. The areas under the curves (AUC) of the receiver operating characteristic curves (ROC) were used to compare the power of these serum lipoprotein ratios markers.

Results: All lipoprotein ratios, lipid profile, blood pressure, and WC were significantly higher in T2D patients as compared to healthy controls ($P<0.05$). TC/HDL-C ratio, TG/HDL-C ratio, non-HDL-C, WC, TG, and TC were significantly correlated with HOMA-IR ($P<0.05$) as obtained by Spearman correlation analysis. The largest AUC of the ROC curve was obtained with the TC/HDL-C ratio as one parameter.

Conclusion: TC/HDL-C ratio, TG/HDL-C, ratio, Non-HDL-C, WC, TG, and TC can be used as the markers of insulin resistance and CVD risk in T2D patients.

Key words HOMA-IR - insulin level - serum lipoprotein ratios - type 2 diabetes mellitus

Type 2 diabetes mellitus (T2D) is part of the metabolic syndrome with a cluster several abnormalities, including insulin resistance, dyslipidemia, cardiovascular disease (CVD)¹⁻⁴. which in part might be due to abnormalities in lipid and lipoprotein metabolism^{5,6}. Dyslipidemia, frequently occurring in T2D patients, might play a critical role in accelerated macrovascular atherosclerotic disease formation and may contribute significantly to the excess

risk of CVD of T2D patients⁷. Dyslipidemia in T2D patients is characterized by elevated triglycerides (TG), reduced high density lipoprotein cholesterol (HDL-C) and small dense low density lipoprotein (LDL)-particles (independent of LDL-cholesterol (LDL-C)), elevated triglyceride-rich remnant lipoprotein (TGRLs), and an increased circulating insulin concentration⁸. In contrast, it appears that a low HDL-C level is independently associated with resistance to insulin-mediated glucose

disposal and compensatory to hyperinsulinemia⁹. characterized by relatively high levels of fasting glucose and insulin. The major quantitative change associated with the insulin resistance syndrome is an elevation in TGRLs, often accompanied by a decreased HDL-C level. Thus, dyslipidemia (by these lipoprotein ratios) may precede the association with insulin resistance and increased risk for CVD. Even the differences in fasting plasma glucose or insulin levels might be useful to identify insulin resistance persons. Obesity, metabolic syndrome, and T2D also show characteristic dyslipidemia⁸⁻¹⁰ and measuring these variables might also help identify insulin resistance. For example, plasma TG, HDL-C, and TC are independently associated with insulin resistance insulin level, and are independent predictors of CVD^{11,12}. The ratios of total cholesterol and TC/HDL-C, triglyceride and TG/HDL-C, LDL-C/HDL-C, as well as the levels of cholesterol retention fraction (CRF), non-HDL-C are simply defined as the difference between total cholesterol and HDL-C, thus, represents cholesterol carried on all of the potentially proatherogenic particles. On this basis, the ratios of TC/HDL-C, TG/HDL-C, LDL-C/HDL-C as levels of CRF [as $[(LDL-C) - (HDL-C)/(LDL-C)]$], non-HDL-C (as TC - HDL-C), LDL-C, TG, and waist circumference (WC) insulin resistance and CVD risk are estimated¹³. A high TG concentration may indicate a high concentration of atherogenic chylomicron and VLDL remnant, and these triglyceride-rich remnants are associated with and increased risk for CVD¹⁴. Insulin resistance can be assessed by using the homeostasis model assessment (HOMA)¹⁵ from fasting serum insulin concentration. HOMA of insulin resistance (HOMA-IR) is a simple, inexpensive, and non-laborious technique. The method derives an estimate of insulin sensitivity from the mathematical modeling of fasting plasma glucose and insulin concentrations.

We investigated the possibility to use the ratios of the levels of TC/HDL-C, TG/HDL-C, LDL-C/HDL-C as well as the levels of CRF, non-HDL-C, LDL-C, TC, and TG, and the WC as surrogates for the estimation of insulin levels and insulin resistance in T2D patients. The power of these parameters of T2D subjects is determined by using receiver operating characteristic (ROC) curves¹⁶.

Material & Methods

Subjects: A total of 92 patients T2D (median age of 61.0 yr), interquartile, 49.3-70.8 yr (71 females with a median age of 59.0 yr, interquartile, 48.5-71.0 yr and 21 males with a median age of 63.0 yr, interquartile,

52.5-70.5 yr) were randomized from the Tapho Primary Health Care Unit, Naresuan University Hospital, during June 2007 through June 2008. These T2D patients were regularly treated with glycemic lowering drugs (glipizide, glibenclamide and/or metformin), lipid lowering drug (hydrochlorothiazine: HCTZ, or simvas or lopid), and anti-hypertensive drug (Atenolol and/or Enalapil). The duration of T2D in these patients was more than 5 yr. The duration of abnormal metabolism in the present study was started at the first year of taken glycemic lowering drugs. The exclusion criteria were CVD or MI, arthritic, pulmonary or other debilitating diseases. All patients with severe microvascular complications and those who currently smoked or had poor glycemic control levels or were on insulin treatment were excluded from the study. In addition, 40 healthy control subjects (12 males, 28 females) had a median age of 64.5 yr (interquartile, 57.8-72.7 yr). These subjects were apparently healthy as based on their medical history and physical examination for diabetes and of the cardiac and vascular systems. The Ethics Committee of the Naresuan University approved the study protocol. All participants gave written informed consent.

Venous blood samples were taken without stasis after a 12 h fast. Fasting plasma glucose (Glu) serum TC, and TG were measured immediately after collection by using enzymatic procedures with a Hitachi 912 autoanalyzer (Roche Diagnostic, Switzerland). HDL-C was measured by a direct method using polyethylene-glycol-pretreated enzymes (Roche Diagnostic, Switzerland). We calculated LDL-C with Friedewald's formula¹⁷. TC/HDL-C ratio was calculated by dividing TC by HDL-C and TG/HDL-C ratio was calculated by dividing TG by HDL-C. The cholesterol retention fraction (CRF) was calculated by dividing the difference of LDL-C and HDL-C by LDL-C¹⁸. Non-HDL-C was calculated by subtracting HDL-C from TC. Serum fasting insulin levels were measured by micro-particle enzyme immunoassay (MEIA) on an automated analyzer (AxSYM, Abbotte Diagnostics, USA). Reproducibility of insulin assay was determined in two samples. Two samples were assayed in replicates for twenty days (n=20 for each sample) using a single lot of reagent and a single calibration. The intra-assay and inter-assay precision were 2.79 per cent CV (mean = 8.6 μ U/ml, SD = \pm 0.24), 3.75 per cent CV (mean = 22.4 μ U/ml, SD = \pm 0.84) and 3.02 per cent CV (mean = 8.6 μ U/ml, SD = \pm 0.26), 4.19 per cent CV (mean = 22.4 μ U/ml, SD = \pm 0.94), respectively. Insulin resistance was estimated with the HOMA-IR, using

fasting insulin and glucose concentrations^{15,19}. HOMA-IR was defined using the following formula: fasting glucose (mmol/l) x fasting insulin (μ U/ml) / 22.5.

Waist circumference (WC) was measured at the midpoint between the rib cage and the top of the lateral border of the iliac crest during minimal respiration. The blood pressure measurements were obtained with the participants in seated position 5 min after resting. Measurements were made twice on all participants at 5 min intervals with a digital blood pressure monitor, ES-P 110 (Terumo cooperation, Japan). The average of the two measurements was used for data analysis.

Statistical analysis: The values are expressed as median and interquartile (Q1-Q3). The Mann-Whitney U test was used to estimate differences between groups. Spearman rank correlation was used to assess the correlation of TC/HDL-C, TG/HDL-C, LDL-C/HDL-C, CRF, non-HDL-C, LDL-C, TG, and WC with insulin levels and insulin resistance. A comparison of TC/HDL-C, TG/HDL-C, LDL-C/HDL-C, CRF, non-HDL-C, LDL-C, TG, and WC in both T2D and non-diabetic were analyzed in terms of a receiver operating characteristic (ROC) curve. A ROC curve is a plot between sensitivity (Y-axis) versus false positive (X-axis), obtained for different cutoff points. Areas under the curve (AUC) of the ROC curves and their 95 per cent confidence intervals (CI) were evaluated as a measure of diagnostic accuracy. A discriminate analysis was performed to identify a combination of these parameters that provided the best differentiation between T2D and non-diabetic individuals. Greater AUC of the ROC curve indicated better markers of the study. In general, an AUC of a ROC of 0.5 suggests no discrimination, whereas a maximal AUC of a ROC of 1 suggests outstanding discrimination¹⁶. All *P*-values < 0.05 (two tailed) were considered as significant. All analyses were performed using the SPSS computer program version 13.0 (SPSS Inc., Chicago, IL).

Results

The laboratory characteristics of the T2D patients and healthy control subjects are shown in Table I, and the baseline characteristics of female and male T2D patients shown in Table II. The 92 patients included in the study had fair glycemic control, none of them obtained an insulin treatment. In this study, 38 (41.3%) had hypertension or systolic BP \geq 140 mmHg and/or diastolic BP \geq 90 mmHg (25 females and 23 males), 45 (48.9%) T2D patients had hypercholesterolemia (TC

\geq 200 mg/dl), 54 (58.7%) had hypertriglyceridemia (TG \geq 150 mg/dl), 26 (33.6%) women had low-HDL-C (\leq 50 mg/dl) and 5 (23.8%) men had low-HDL-C (\leq 40 mg/dl), 33 (46.5%) women and 8 (38.1%) men had both hypercholesterolemia (TC \geq 200 mg/dl) and hypertriglyceridemia (TG \geq 150 mg/dl), 7 (9.9%) women had hypercholesterolemia, hypertriglyceridemia, and low HDL (<50 mg/dl), 14

Table I. Baseline characteristics of type 2 diabetic patients and healthy control subjects. The values are shown as medians and interquartiles (Q1-Q3)

Variables	T2D patients (n=92)	Healthy controls (n=40)	<i>P</i> value
Age (yr)	61.0	64.5	0.105
Q1-Q3	49.3-70.8	57.8-72.7	
Systolic BP (mmHg)	131.5	126.5	0.033
Q1-Q3	120.3-144.8	114.0-135.2	
Diastolic BP (mmHg)	78.5	74.5	0.002
Q1-Q3	72.0-90.0	70-80.0	
BMI (kg/m ²)	26.2	23.6	<0.001
Q1-Q3	23.5-28.6	20.9-26.0	
Waist circumference (cm)	88.0	83.4	<0.001
Q1-Q3	84.0-92.0	78-89	
Glucose (mg/dl)	131.0	80.0	<0.001
Q1-Q3	99.0-158.0	76.0-90.0	
Total cholesterol (mg/dl)	197.5	178.0	0.002
Q1-Q3	168.0-226.8	165.3-193.3	
Triglycerides (mg/dl)	166.0	126	<0.001
Q1-Q3	115.3-279.0	101.3-170.8	
HDL-C (mg/dl)	50.2	59.7	<0.001
Q1-Q3	42.6-55.9	52.3-68.1	
LDL-C (mg/dl)	111.9	92.3	<0.001
Q1-Q3	85.7-129.8	78.6-101.4	
TC/HDL-C ratio	4.17	2.96	<0.001
Q1-Q3	3.27-4.94	2.52-3.53	
TG/HDL-C ratio	3.41	2.31	<0.001
Q1-Q3	2.48-5.84	1.50-2.98	
LDL-C/HDL-C ratio	2.30	1.52	<0.001
Q1-Q3	1.69-2.88	1.16-1.99	
Cholesterol retention fraction (CRF)	0.57	0.34	<0.001
Q1-Q3	0.41-0.65	0.14-0.50	
Non-HDL-C (mg/dl)	150.9	119.60	<0.001
Q1-Q3	113.2-178.7	105.4-131.3	
Insulin level (μ U/ml)	8.85	5.35	<0.001
Q1-Q3	5.9-12.7	3.85-7.13	
Insulin resistance (HOMA-IR)	2.99	1.08	<0.001
Q1-Q3	1.79-4.04	0.73-1.44	

(19.7%) women had hypertriglyceridemia, and low HDL (<50 mg/dl), 1 (4.8%) men had hypercholesterolemia, hypertriglyceridemia, and low HDL (<40 mg/dl), 2 (9.5%) men had hypertriglyceridemia, and low HDL (<40 mg/dl). TC/HDL-C, TG/HDL-C, LDL-C/HDL-C, CRF, non-HDL-C, LDL-C, TG, TC, WC, HOMA-IR and insulin levels were significantly higher in T2D patients as compared to control subjects, and HDL-C was significantly lower in T2D patients than

Table II. Baseline characteristics of male and female type 2 diabetic patients. The values are shown as medians and interquartiles (Q1-Q3)

Variables	Male T2D patients (n=21)	Female T2D patients (n=71)	P value
Q1-Q3	52.5-70.5	48.0-71.0	
Systolic BP (mmHg)	135.0	129.0	0.019
Q1-Q3	128.5-164.0	116.0-142.0	
Diastolic BP (mmHg)	90.0	77.0	0.003
Q1-Q3	79.0-98.5	71.0-86.0	
BMI (kg/m ²)	25.7	26.4	0.131
Q1-Q3	22.6-27.7	24.4-28.9	
Waist circumference (cm)	92.0	88.0	0.258
Q1-Q3	85.5-93.0	84.0-91.0	
Glucose (mg/dl)	128.0	132.0	0.652
Q1-Q3	93.5-176.0	103.0-158.0	
Total cholesterol (mg/dl)	204.0	194.0	0.609
Q1-Q3	163.0-225.0	168.0-228.0	
Triglycerides (mg/dl)	139.0	167.0	0.570
Q1-Q3	101.5-339.0	125.0-279.0	
HDL-C (mg/dl)	43.9	51.5	<0.001
Q1-Q3	40.4-47.1	44.0-58.4	
LDL-C (mg/dl)	124.9	110.4	0.074
Q1-Q3	103.9-136.4	78.9-125.9	
TC/HDL-C ratio	4.88	3.86	0.008
Q1-Q3	3.99-5.53	3.18-4.74	
TG/HDL-C ratio	3.08	3.47	0.580
Q1-Q3	2.45-8.43	2.46-5.08	
LDL-C/HDL-C ratio	2.89	2.11	0.001
Q1-Q3	2.38-3.28	1.51-2.69	
Cholesterol retention fraction (CRF)	0.65	0.53	0.001
Q1-Q3	0.58-0.69	0.34-0.63	
Non-HDL-C (mg/dl)	158.0	147.9.6	0.225
Q1-Q3	124.4-180.8	110.5-175.9	
Insulin level (μU/ml)	7.4	8.9	0.293
Q1-Q3	3.9-15.6	6.5-12.1	
Insulin resistance (HOMA-IR)	2.39	3.04	0.364
Q1-Q3	0.97-6.24	2.03-3.95	

control subjects ($P<0.05\%$) with the Mann-Whitney U test. TC/HDL-C ratio, TG/HDL-C ratio, non-HDL-C, WC, TG and TC were significantly correlated with HOMA-IR ($r=0.312$, $P<0.002$; $r=0.463$, $P<0.001$; $r=0.339$, $P=0.001$, $r=0.208$, $P=0.047$, $r=0.490$, $P<0.001$, $r=0.294$, $P=0.004$, respectively), and with insulin level ($r=0.238$, $P=0.006$, $r=0.417$, $P<0.001$;

Table III. The correlation of TC/HDL-C ratio, TG/HDL-C ratio, LDL-C/HDL-C ratio, CRF, non-HDL-C, LDL-C, TG, and WC insulin resistance (HOMA-IR) and insulin levels in T2D patients by Spearman's rank correlation analysis

	Insulin levels		Insulin resistance (HOMA-IR)	
	r	P value	r	P value
TC/HDL-C ratio	0.283	0.006*	0.312	0.002*
TG/HDL-C ratio	0.417	<0.001*	0.463	<0.001*
Non-HDL-C	0.251	0.016*	0.339	0.001*
CRF	0.131	0.213	0.134	0.201
LDL-C/HDL-C ratio	0.131	0.213	0.134	0.201
LDL-C	0.040	0.704	0.086	0.412
TG	0.410	<0.001*	0.490	<0.001*
TC	0.186	0.075	0.294	0.004*
WC	0.243	0.02*	0.208	0.047*

*, significance $P<0.05$

Table IV. The area under the receiver-operating characteristic curves for the insulin resistance (HOMA-IR) and insulin levels markers for type 2 diabetic patients ($P<0.001$)

Markers	Area under the ROC curve \pm SE	95% Confidence interval	P value
TC/HDL-C ratio	0.796 \pm 0.04	0.717 - 0.876	<0.001
TG/HDL-C ratio	0.760 \pm 0.04	0.676 - 0.843	<0.001
Non-HDL-C	0.737 \pm 0.04	0.651 - 0.822	<0.001
WC	0.701 \pm 0.05	0.599 - 0.803	<0.001
TG	0.691 \pm 0.05	0.602 - 0.781	<0.001
TC	0.671 \pm 0.05	0.580 - 0.762	0.002

SE, standard error

Table V. The cutoff points corresponding to the highest %sensitivity and %specificity were calculated from the ROC curves for the detection of insulin levels and insulin resistance in T2D

Markers	Cut-off point	T2D patients	
		Sensitivity (%)	Specificity (%)
TC/HDL-C ratio	3.58*	71.7	77.5
TG/HDL-C ratio	2.48*	75.0	60.0
Non-HDL-C (mg/dl)	130.4*	67.4	75.0
WC (cm)	84.8*	73.9	65.0
TG (mg/dl)	148.5*	59.8	60.0
TC (mg/dl)	189.5*	57.6	67.5

*cut-off value in highest sensitivity and specificity

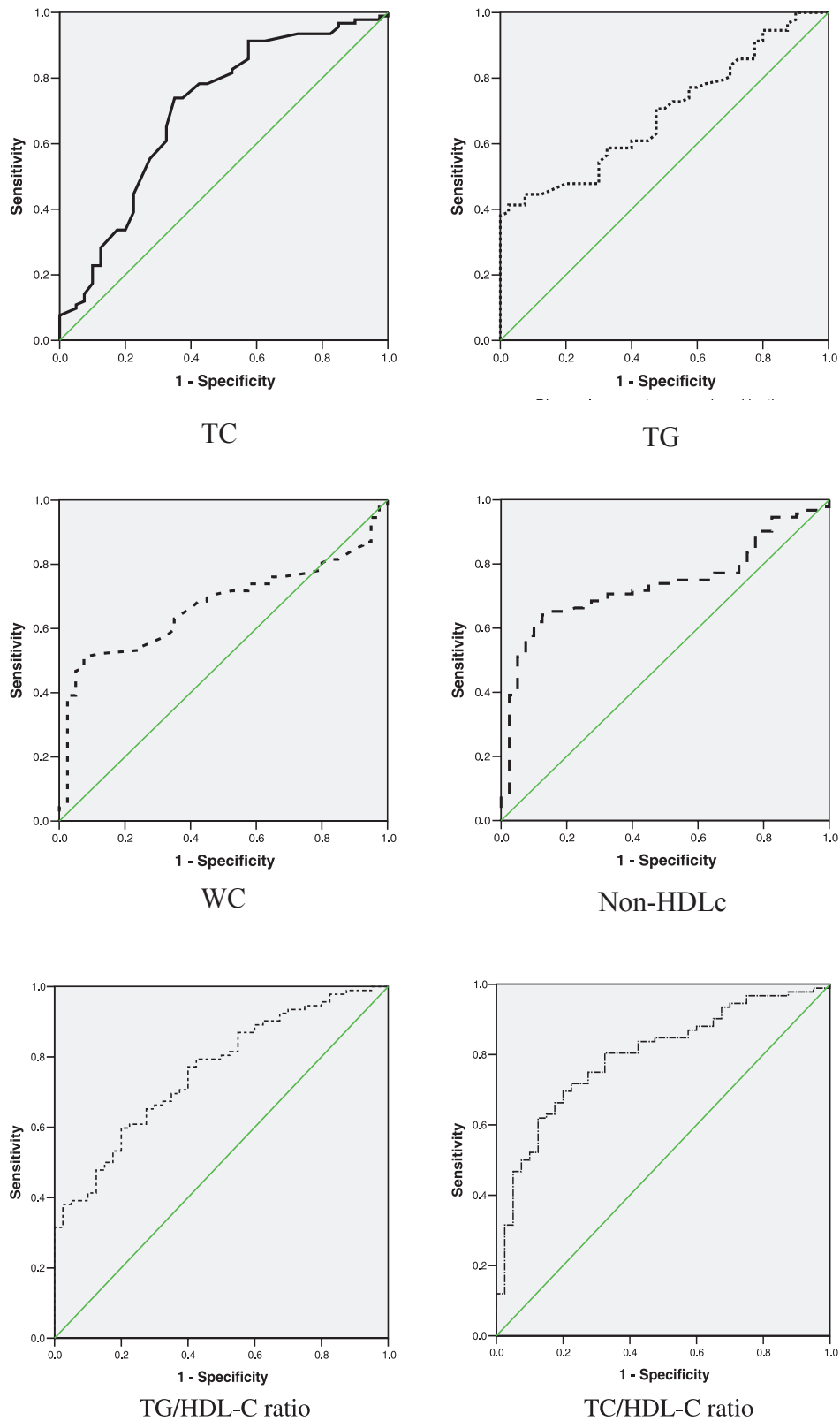


Fig. ROC curves for TC, TG, WC, Non-HDL-C, TG/HDL-C ratio, and TC/HDL-C ratio. The area under the ROC curves was 0.671, 0.691, 0.701, 0.760, and 0.796 for the insulin resistance (HOMA-IR) prediction, respectively. Diagonal segments are produced by ties.

$r=0.251$, $P=0.016$; $r=0.410$, $P<0.001$, $r=0.243$, $P=0.02$, respectively, except TC was not significantly correlated with insulin level) with the Spearman correlation analysis (Table III). We plotted the ROC curves for TC/HDL-C ratio, TG/HDL-C ratio, non-HDL-C, WC, TG, and TC. The results of TC/HDL-C ratio, TG/HDL-C ratio, non-HDL-C, WC, TG, and TC ROC curve analysis showed that each marker is a significant discriminator for HOMA-IR. The AUC of the ROC curves were used for prediction of better markers for insulin resistance (HOMA-IR) and insulin level in T2D patients. The largest AUC was obtained with the TC/HDL-C ratio, indicating that the model with this ratio was superior for estimating the insulin resistance (HOMA-IR) of T2D patients in this study (Table IV, Fig.). The relationship between TC/HDL-C ratio, TG/HDL-C ratio, non-HDL-C, WC, TG and TC with HOMA-IR, the optimal TC/HDL-ratio, TG/HDL-C ratio, non-HDL-C, WC, TG, and TC cut-off for prediction of HOMA-IR in present study were 3.58 with sensitivity and specificity of 71.7 and 77.5 per cent; 2.48 with sensitivity and specificity of 75 and 60 per cent; 130.35 mg/dl with sensitivity and specificity of 67.4 and 75 per cent; 84.75 cm with sensitivity and specificity of 73.9 and 65 per cent; 148.5 mg/dl with sensitivity and specificity of 59.8 and 60 per cent; 189.5 mg/dl with sensitivity and specificity of 57.6 and 67.5 per cent, respectively (Table V).

Discussion

Our study aimed to find a simple approach to identify apparently healthy patients who were insulin resistant and at an increased risk of CVD and other clinical syndromes related to defect in insulin action. Because of its simple calculations, the TC/HDL-C ratio, TG/HDL-C ratio, and non-HDL-C levels are easily available to the clinician with every lipid profiles ordered, thus eliminating any additional costs. T2D is also frequently associated with vascular complications and dyslipidemia. The major features are initially recognized hypertriglyceridemia, decreased levels of HDL-C, and normal or elevated levels of LDL-C with an altered composition²⁰. These appear to be problems of VLDL and HDL particles but not of LDL particles, and increases in circulating insulin concentration. In contrast, it appears that a low HDL-C level is independently associated with resistance to insulin-mediated glucose disposal and compensatory hyperinsulinemia²¹. All of these features have individually been implicated as contributors to coronary heart disease (CHD). In the present study

TC/HDL-C ratio, TG/HDL-C ratio, non-HDL-C, WC, TG, and TC were associated with insulin resistance (HOMA-IR) in T2D patients with Spearman's correlation analyses. All of these markers had an AUC of the ROC of greater than 0.5, thus those were useful markers for insulin resistance (HOMA-IR) in T2D patients. Our study suggests that TC/HDL-C ratio, TG/HDL-C ratio, non-HDL-C, WC, TG, and TC can be used as markers for insulin resistance (HOMA-IR) and CVD risk in T2D patients¹³. The cut-off value of TC/HDL-C ratio in our study were lower than in the recent reports in the Western populations²²⁻²⁷.

An assessment of atherosclerotic risk in T2D patients requires close attention to lipid screening. T2D patients are at risk with cardiovascular disease⁴ may be due to abnormalities in lipid and lipoprotein metabolism²⁸ due to insulin resistance^{29,30}. The major quantitative change associated with the insulin resistance syndrome is an elevation in TGRLs, often accompanied by a decreased HDL-C level. Insulin plays a key role in TG metabolism as it normally reduces availability of large TGRLs particles, synthesized by a distinct pathway compared with smaller VLDL particles³¹. In diabetes subjects, insulin fails to suppress synthesis of large VLDL particles³². In addition, insulin resistance is associated with increased flow of free fatty acid to liver, increased lipid synthesis in the liver, and decreased clearance of VLDL particles, all of which increase VLDL concentrations in plasma³³. Thus, dyslipidemia (by these lipoprotein ratios) may precede the association with insulin resistance and increased risk for CVD. Indeed, the insulin level and insulin resistance were significantly predicted by these markers in our study. This does not mean that insulin resistance is a predictor of CVD, but rather that the cluster of abnormalities associated with insulin resistance may be very important in this context. All of these lipoprotein ratios may use as CVD risk markers and management in the dyslipidemia in T2D and the metabolic syndrome, and may useful for improved their treatment of hyperglycemia, dyslipidemia, and to protect their beta-cells.

Our study showed that TC/HDL-C, TG/HDL-C, Non-HDL-C, WC, TG, and TC were significantly correlated with insulin resistance (HOMA-IR) in T2D patients. The combination of these evaluated markers may identify a group of patients with a more marked risk for insulin resistance and cardiovascular disease risk.

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