Original Article

The difference in correlation between insulin resistance index and chronic inflammation in type 2 diabetes with and without metabolic syndrome

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Abstract

Background: Insulin resistance (IR) is associated with low-grade systemic inflammation. It plays an important role in the pathogenesis of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) in patients with metabolic syndrome (MetS). It is unclear whether diabetic patients with MetS confer elevated CVD risk and outcomes beyond the impact of individual's components of MetS. The aim of this study is to highlight the central role of IR, inflammation, triglyceride/high-density lipoprotein- cholesterol (TG/HDL-C) ratio, and atherogenic index of plasma (AIP) in T2DM with MetS.

Materials and Methods: This cross-sectional study comprised 130 men distributed into three groups, namely Controls: 40 nondiabetic healthy volunteers; Group I: 40 T2DM patients without MetS, and Group II: 50 T2DM patients with MetS. Fasting blood samples were collected for the measurement of blood lipid profile, glucose, insulin, hemoglobin A1c, and high-sensitivity C-reactive protein (hs-CRP). TG/HDL-C ratio, AIP, and homeostasis model assessment of insulin resistance (HOMA-IR) were calculated.

Results: Significant positive association was observed between HOMA-IR and hs-CRP only in Group II and between HOMA-IR and TG/HDL-C ratio in all subjects. Significant differences were seen in waist and hip circumferences, waist/hip ratio, body mass index, systolic blood pressure, fasting blood glucose, TGs, HDL-C, insulin, hs-CRP, HOMA-IR, TG/HDL ratio, and AIP between Controls and Group I with Group II.

Conclusions: In T2DM with MetS, coexistence of elevated atherogenic indices, systemic inflammation, and association between HOMA-IR and TG/HDL-C ratio were seen. These factors are considered having important role in elevated CVD risk beyond MetS components in these patients.

Key Words: Atherogenic index of plasma, inflammation, insulin resistance index, metabolic syndrome, triglyceride/high-density lipoprotein -cholesterol ratio, type 2 diabetes mellitus

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INTRODUCTION

Metabolic syndrome (MetS) is a complex of modifiable risk factors including hyperglycemia, hypertension, hypertriglyceridemia, decreased high-density lipoprotein cholesterol (HDL-C), and

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abdominal obesity.[1] MetS, visceral obesity, and insulin resistance (IR) are considered to have major role in the pathogenesis of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).[2,3] It has been hypothesized that IR state is linked to chronic low-grade inflammation.[4] Inflammation links obesity to IR via the inhibition of the insulin receptor signaling cascade.[5,6] Chronic low-grade systemic inflammation (as either a cause or effect) plays an important role on the onset and disease progression as well as development of micro- and macro-vascular dysfunction in T2DM.[7,8] In addition, a strong association has been described between systemic inflammation and CVD risk, independent of other established risk factors.[9,10]

Many studies have shown that T2DM patients with MetS are at greater risk of coronary heart disease (CHD) compared with those without MetS. Although individual components of MetS contribute to increased cardiovascular risk, it is unclear whether the MetS confers elevated CVD risk beyond the impact of its components.[11,12]

In T2DM patients, an abnormal lipid profile contributes to atherosclerosis and atherosclerosis accounts for as many as 75–80% of mortality in these patients.[13] High ratio of triglyceride (TG) to HDL-C (TG/HDL-C) ratio indicates an atherogenic lipid profile and is a powerful independent risk for cardiovascular events.[14,15] Recent studies suggest that TG/HDL-C ratio may serve as a simple and useful tool for identify apparently healthy individuals who are IR and at high cardiometabolic risk. In addition, the ratio may be an index of CHD mortality and of incidence of T2DM in men.[16] A large number of clinical studies make attempt to introduce a better marker of atherogenic dyslipidemia that can predict the risk of CVD and to be useful for evaluating response to treatment instead of the classical ratio. Tan *et al*. used the atherogenic index of plasma (AIP), calculated as log (TG/HDL-C), with TG and HDL-C expressed in molar concentrations. AIP reflects the true relationship between protective and atherogenic lipoprotein and is associated with the size of pre- and anti-atherogenic lipoprotein particle and esterification. It has been shown that AIP is a strong marker to predict the risk of atherosclerosis and CHD.[17]

Many studies have found an association between elevated high-sensitivity C-reactive protein (hs-CRP) levels and homeostasis model assessment of insulin resistance (HOMA-IR);[7,18,19] however, the difference in the association between HOMA-IR and hs-CRP in T2DM with and without MetS has not been investigated in previous studies. In T2DM with MetS, elevated atherogenic TG/HDL-C ratio and AIP, systemic inflammation, and the association between HOMA-IR and TG/HDL-C ratio may underline elevated CVD risk beyond the impact of MetS components. The aim of this study is to highlight the central role of IR, inflammation, TG/HDL-C ratio, and AIP other than MetS components, in T2DM with MetS.

MATERIALS AND METHODS

Study population and design

This cross-sectional study was performed in Isfahan Cardiovascular Research Center in 2014. For this study, 130 men between 40 and 60 years of age were recruited. Subjects were distributed into three groups, namely Control group: Including 40 normoglycemic healthy subjects; Group I: 40 T2DM without MetS and apparent signs of complication; and Group II: 50 T2DM with MetS. Diagnosis of T2DM was established using the criteria proposed by American Diabetes Association (fasting glucose ≥126 mg/dl or 2 h postprandial glucose ≥200 mg/dl before diagnosis and treatment[20] or the self-reported use of antidiabetic medications but not insulin). Subjects with infections, inflammatory diseases, corticosteroids medications, lipid-lowering drug (such as gemfibrozil and clofibrate), smoking cigarettes, or other tobacco products were excluded from the study. Written informed consent was obtained from each participant, and the study was approved by the Ethics Committee of Isfahan University of Medical Sciences.

Criteria for subject classification

According to National Cholesterol Education Program (Adult Treatment Panel III) criteria, MetS is present when 3 or more of the following determinants are met: Increased waist circumference (WC ≥102 cm for men and ≥88 cm for women), hyperglycemia (fasting plasma glucose ≥100 mg/dl), hypertriglyceridemia (TGs ≥150 mg/dl), low HDL-C (HDL-C <40 mg/dl for men and <50 mg/dl for women), and blood pressure elevation (≥130/85 mmHg).[21] IR was estimated using the HOMA-IR index as HOMA-IR = fasting serum insulin (FINS) (μU/ml) × fasting plasma glucose (mmol/l)/22.5.[22] The plasma concentration ratio of TG to HDL-C was calculated and the cardiometabolic risk profile of "high risk" individuals identified by TG/HDL-C ratios ≥3.5 in men and ≥2.5 in women.[23] AIP, calculated as log (TG/HDL-C), with TG and HDL-C expressed in molar concentrations. An AI*P* value of under 0.11 is associated with low risk of CVD; the values between 0.11 and 0.21 and upper than 0.21 are associated with intermediate and increased risks, respectively.[24] The serum hs-CRP level was classified as <1, 1–3, and ≥3 mg/l as lower, moderate, and higher cardiovascular risk, respectively.[25]

Data collection

Weight and height of participants were determined in light clothing and without shoes by portable calibrated electronic weighing scale and portable measuring inflexible bars, respectively. WCs and hip circumferences (HCs) measured on subjects according to standard conditions using a measuring tape, and then waist/hip circumference ratio (WHR) was calculated. Body mass index (BMI) was calculated as weight of individuals divided by the square of their height (kg/m^2). Systolic and diastolic blood pressures (SBP and DBP) were measured after a rest for 15 min using a sphygmomanometer; the mean of three measurements of SBP and DBP at intervals of 2–5 min was considered the blood pressure. All measurements were taken by the same person to avoid subjective error.

Laboratory analysis

Venous blood samples were obtained after at least 10 h overnight fasting from the subjects by venipuncture and collected in ethylenediaminetetraacetic acid and plain test tubes. Fasting blood glucose (FBG) was measured by enzymatic colorimetric method using glucose oxidase test. Serum total cholesterol (TC), TGs, and HDL-C were determined by enzymatic methods using commercial kits and a Hitachi 902 automated analyzer. Serum low-density lipoprotein-cholesterol (LDL-C) was calculated using Friedewald's formula.[26] When serum TGs concentration was >400 mg/dl, LDL-C was determined directly by enzymatic method using a commercial kit. Hemoglobin A1c (Hb A1c) was analyzed by latex immunoturbidimetric method. FINS level was measured using an enzyme-linked immunosorbent assay (ELISA) kit (Monobound Company, USA), and hs-CRP was measured with a latex-enhanced immunoturbidimetric assay using an automated analyzer.

Statistical analysis

Statistical analyses on data were performed using the IBM SPSS Statistics 20 (USA). The results were expressed as mean ± standard deviation unless otherwise indicated. The normal distribution of the variable was checked by Kolmogorov–Smirnov test. The equality of variances was calculated with the Levene's test. Differences between groups were assessed by independent samples *t*-tests for continuous variables and Mann–Whitney U-test for nonparametric variables such as DBP. The association between variables was investigated using bivariate correlation analysis. The correlations between quantitative variables were studied with the Pearson's correlation for parametrical variables and Spearman test for nonparametric variables. $P < 0.05$ was considered significant.

RESULTS

Clinical and biochemical characteristics of the study subjects are presented in Table 1.

TGs was significantly elevated in Group II patients compared to both Group I (P = 000) and Control groups (P = 000). There was no significant difference in TGs levels between Group I patients and Controls (P = 0.129). Similarly, FINS levels were significantly higher in Group II patients compared to both Group I (P = 0.007) and Control groups (P = 0.029). There was no significant difference in FINS levels between Group I patients and Controls (P = 0.750). Group II had significantly higher FBG levels than Group I (P = 034) and Control group (P = 000). Hb A1c was significantly elevated in both Group I and Group II patients compared to Controls (P = 000 and P = 000, respectively). There was no significant difference in Hb A1c levels between Group I and Group II patients (P = 0.798). hs-CRP levels were significantly higher in Group II patients compared to both Group I (P = 0.049) and Control groups (P = 0.019). There was no significant difference in hs-CRP and AIP levels between Group I patients and Controls (P = 0.501 and P = 0.116, respectively). HDL-C levels were significantly lower in Group II patients compared to both Group I (P = 000) and Control groups (P = 000) and in Group I patients compared to Controls (P = 0.016). WC, HC, WHR, BMI, SBP, and AIP values were significantly higher in Group II patients compared to both Group I (P = 0.001, 0.012, 0.010, 0.050, 000, and 000, respectively) and Control groups (P = 000, 000, 0.007, 0.002, 0.026, and 000, respectively). Significance differences were seen in FBG and DBP between the Controls and Group I (P = 000 and P = 010, respectively). No significance differences were seen between the Controls and Group I with regards to weight, WC, HC, WHR, BMI and SBP (P > 0.05). No significant differences in age and TC and LDL-c levels were seen in the three study groups.

Table 2 presents the Pearson correlation coefficients between hs-CRP and HOMA-IR with components of MetS in all the subjects. Significant positive correlations were found between HOMA-IR and FBG (r = 0.671, P = 0.000), TGs (r = 0.269, P = 0.002), WC (r = 0.326, P = 0.000), and negative correlation with HDL-C (r = −0.244, P = 0.005). Significant positive correlations were seen between hs-CRP and FBG (r = 0.161, P = 0.049), TGs (r = 0.175, P = 0.034), and WC (r = 0.357, P = 0.000).

Figure 1 depicts the comparative values for HOMA-IR and TG/HDL ratio for T2DM groups compared with Controls. The mean values (±standard error of the mean)

Table 1: Clinical and biochemical characteristics of the study subjects

Variables	Controls	Group I	Group II	*P* value Group I versus controls	*P* value Group II versus controls	*P* value Group II versus Group I
Age (years)	50.02±9.8	50.27±10.1	53.58±9.6	0.487	0.232	0.642
weight (kg)	75.29±12.6	80.27±12.1	84.24±12.3	0.075	**0.001**	0.129
WC (cm)	93.78±10.7	98.20±11.2	105.36±9.4	0.082	**0.000**	**0.001**
HC (cm)	99.04±8.2	102.11±7.0	105.98±7.1	0.082	**0.000**	**0.012**
WHR	0.94±0.1	0.96±0.1	0.99±0.1	0.570	**0.007**	**0.010**
BMI (kg/m^2)	22.38±3.6	23.40±3.2	24.79±3.4	0.191	**0.002**	**0.050**
SBP (mmHg)	122.05±9.0	121.82±8.8	130.1±13.5	0.233	**0.026**	**0.000**
DBP (mmHg)	82.22±7.1	79.8±6.6	80.5±13.8	**0.010**	0.464	0.334
TGs (mg/dL)	119.05±30.5	132.60±46.2	199.10±85.1	0.129	**0.000**	**0.000**
TC (mg/dL)	195.05±35.2	184.42±33.7	187.56±44.5	0.172	0.387	0.713
HDL-C (mg/dL)	47.63±5.7	43.85±7.8	35.82±6.1	**0.016**	**0.000**	**0.000**
LDL-C (mg/dL)	118.12±28.1	114.92±27.0	112.66±34.5	0.606	0.410	0.735
AIP	0.037±0.032	0.103±0.025	0.353±0.028	0.116	**0.000**	**0.000**
FBG (mg/dL)	97.48±10.0	139.95±48.8	160.92±43.3	**0.000**	**0.000**	**0.034**
HbA1c (%)	5.48±0.4	7.53±1.5	7.63±1.7	**0.000**	**0.000**	0.798
FINS (mU/L)	10.87±5.3	10.53±4.1	13.85±6.9	0.750	**0.029**	**0.007**
hs-CRP (mg/L)	1.41±1.1	1.62±1.4	2.11±1.4	0.501	**0.019**	**0.049**

Data are expressed as mean±SD and analyzed using independent-Samples *t*-test for continuous variable and Mann-Whitney U-test for nonparametric variables. Significant *P* values are shown in bold. AIP: Atherogenic index of plasma, BMI: Body mass index, DBP: Diastolic blood pressure, FBG: Fasting blood glucose, FINS: Fasting serum insulin, HbA1C: Hemoglobin A1C, HC: Hip circumference, HDL-C: High-density lipoprotein-cholesterol, hs-CRP: High-sensitivity C-reactive protein, LDL-C: Low-density lipoprotein-cholesterol, SBP: Systolic blood pressure, TC: Total cholesterol, TGs: Triacylglycerols, WC: Waist circumference, WHR: Waist-hip ratio

Table 2: Pearson correlation coefficient between homeostatic model assessment-insulin resistance and high sensitivity C-reactive protein with metabolic syndrome component in all subjects

Variables	FBG	TG	HDL-C	SBP	DBP	WC
HOMA-IR	0.671	0.269	−0.244	−0.084	−0.098	0.326
P	**0.000**	**0.002**	**0.005**	0.345	0.270	**0.000**
hs-CRP	0.161	0.175	−0.100	−0.006	0.079	0.357
P	**0.049**	**0.034**	0.226	0.944	0.336	**0.000**

Data are expressed as mean±SD. Significant *P* values are shown in bold. SD: Standard deviation, HOMA-IR: Homeostatic model assessment-insulin resistance, hs-CRP: High-sensitivity C-reactive protein, FBG: Fasting blood glucose, TG: Triacylglycerol, HDL-C: High-density lipoprotein cholesterol, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, WC: Waist circumference

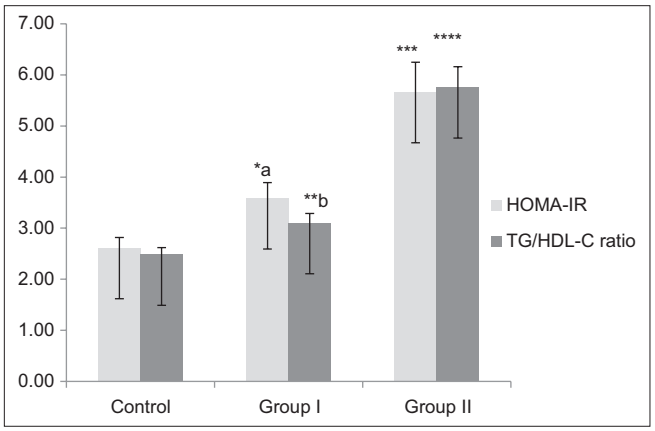

Figure 1: Comparison of HOMA-IR and TG/HDL ratio for different groups. Data are expressed as mean ± SEM. *GI vs. Controls (*P* = 0.008), **GI vs. Controls (*P* = 0.008), *** GII vs. Controls (*P* = 0.000), ****GII vs. Controls (*P* = 0.000), a GI vs. GII (*P* = 0.002), b GI vs. GII (*P* = 0.000)

of HOMA-IR and TG/HDL ratio in Controls (2.62 ± 0.2 and 2.49 ± 0.13, respectively) were significantly different compared to both Group I (3.59 ± 0.3 and 3.11 ± 0.18, respectively) (*P* = 0.008 for both HOMA-IR and TG/HDL ratio) and Group II (5.67 ± 0.58 and 5.76 ± 0.4, respectively) (*P* = 0.000 both HOMA-IR and TG/HDL ratio). There was also significant difference in HOMA-IR and TG/HDL ratio between Groups I and II (*P* = 0.002 and *P* = 0.000, respectively).

Significant positive correlations of TG/HDL ratio with HOMA-IR in all subjects is depicted in Figure 2 (*r* = 0.304 and *P* = 0.000). The correlation of HOMA-IR with hs-CRP in each group was determined by Pearson correlation coefficient and scatter diagrams were obtained in [Figure 3a-c]. There was no correlation between HOMA-IR with hs-CRP in Controls [Figure 3a, *r* = 0.045 and *P* = 0.801] and Group I [Figure 3b, *r* = 0.122 and *P* = 0.485], while there was significant positive correlation between HOMA-IR and hs-CRP in Group II [Figure 3c, *r* = 0.349 and *P* = 0.020].

DISCUSSION

Our analysis provides evidence for a significant positive association between HOMA-IR and hs-CRP levels only in Group II. Previous studies also indicated the association between HOMA-IR and hs-CRP levels in subjects with diabetes and MetS.[27,28] However, these studies did not examine this association in T2DM with and without MetS at the same time. In Group II, the observed association between HOMA-IR

and hs-CRP levels and elevated low-grade systemic inflammation, compared with Group I and Controls, highlight coexistence of systemic inflammation and IR and suggest as IR increases, hs-CRP also increases.

Elevation in the ratio of TG/HDL-C and AIP, as atherogenic indices for CVD risks, has proven to be powerful independent predictors of coronary CHD.[16,17,24] Results of this study show the association between TG/HDL-C ratio and HOMA-IR in all subjects and a high TG/HDL-C ratio in T2DM subjects compared to Controls. Although there is overlap between TG/HDL-C ratio and MetS, almost half of individuals with a high ratio did not meet MetS.[17]

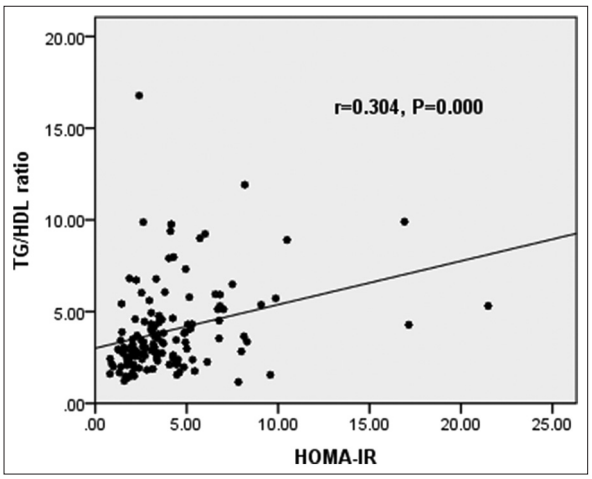

Figure 2: Correlation of TG/HDL ratio with HOMA-IR in all subjects

Previous studies suggest that MetS may be associated with an increasing risk of future cardiovascular events.[29,30] The magnitude of this association, however, seems to be strongly affected by the presence of inflammation and the atherogenic profile of TG/HDL ratio and AIP.

The cardiometabolic risk profile of "high risk" individuals identified by TG/HDL-C ratios ≥3.5 in men and the serum hs-CRP level classification as <1, 1–3, and ≥3 mg/l have been defined as lower, moderate, and higher cardiovascular risk.[23,24] Using these criteria, in Controls, 40.5% subjects had a low hs-CRP level, 48.7% had an intermediate hs-CRP level, and 10.8% had an elevated hs-CRP level; in addition, 90% had TG/HDL ratio <3.5 and 10% TG/HDL ratio >3.5. Among Group I patients, 46.2% had a low hs-CRP level, 38.4% had an intermediate hs-CRP level, and 15.4% had an elevated hs-CRP level; in addition, 67.5% had TG/HDL ratio <3.5 and 32.5% TG/HDL ratio >3.5. However, in Group II patients, 21.7% had a low hs-CRP level, 54.4% had an intermediate hs-CRP level, and 23.9 had an elevated hs-CRP level; in addition, 20% had TG/HDL ratio <3.5 and 80% TG/HDL ratio >3.5.

These findings may suggest that MetS confers elevated CVD risk beyond the sum of its components. This

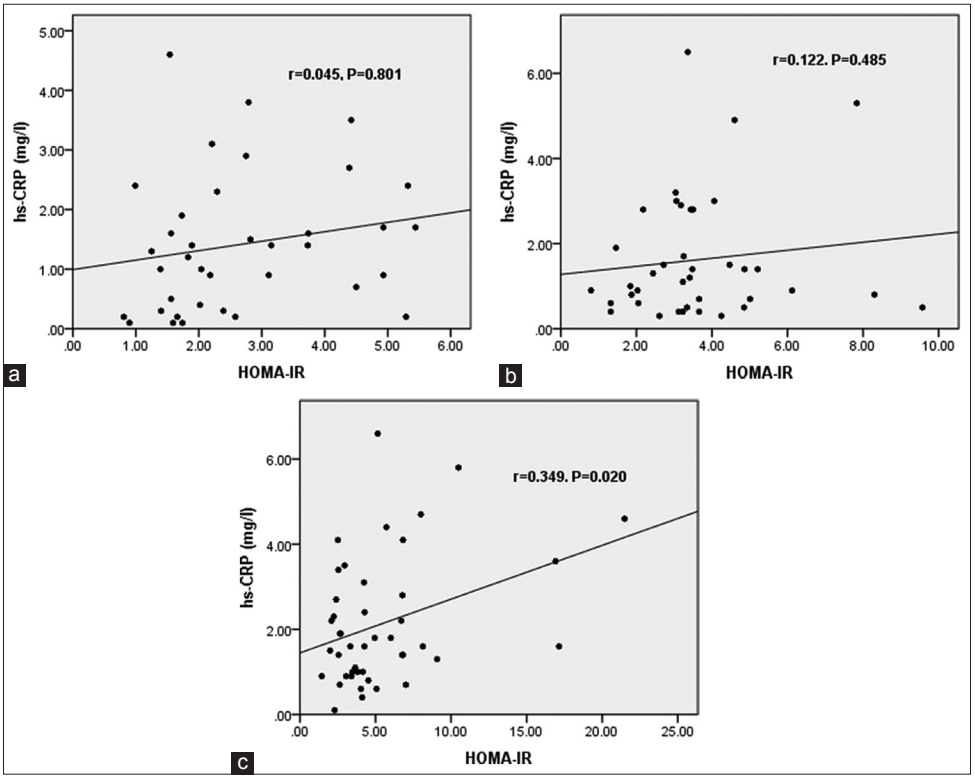

Figure 3: Correlation between HOMA-IR and hs-CRP in (a) Controls (b) Group I and (c) Group II

could be a reason for the higher prevalence of CVD in people with T2DM and MetS compared with those with diabetes without MetS.[11]

Consistent with earlier observations, we found correlation between HOMA-IR and hs-CRP with component of MetS, but not all of the components of MetS are correlated with the level of hs-CRP.[31,32] Among the five components of MetS, only FBG, TGs, and WC were correlated with hs-CRP levels.

Limitations of the present study are its cross-sectional design, so the association of hs-CRP with HOMA-IR in T2DM with MetS needs to be further explored in the longitudinal study. In this study, there were not enough data available on CVD, because our study population was T2DM patients without any vascular complication; therefore, the associations of the level of hs-CRP with CVD were not assessed.

CONCLUSIONS

In T2DM with MetS, systemic inflammation, elevated atherogenic indices, and positive correlation between HOMA-IR and TG/HDL-C ratio have important role in elevated CVD risk beyond impact of MetS components. It is relatively simple to assess the serum level of hs-CRP, TG/HDL-C ratio, and AIP as useful clinical measures for early detection of individuals at risk for IR, MetS, and CVD. Thus, we hope that the current findings will thereby increase identification and disease management of high-risk T2DM patients to prevent cardiac events.

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Conflicts of interest

There are no conflicts of interest.

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