original article

Metabolic syndrome in drug-naïve Chinese patients with insulin-sensitive and insulin-resistant type 2 diabetes

Jiunn-Diann Lin,[a] Chang-Hsun Hseih,[b] Wei-Cheng Lian,[c] Dee Pei,[d] Yao-Jen Liang,[e] Yen-Lin Chen[f]

From the [a]Division of Endocrinology, Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University; Division of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [b]Division of Endocrinology and Metabolism, Department of Internal Medicine, Tri-Service General Hospital, Taipei, Taiwan; [c]Division of Endocrinology and Metabolism, Department of Internal Medicine, Buddhist Dalin Tzu Chi General Hospital and College of Medicine, Tzu Chi University, Hualien City, Taiwan; [d]Division of Endocrinology and Metabolism, Department of Internal Medicine, Cardinal Tien Hospital, Medical School, Catholic Fu Jen University, New Taipei City, Taiwan; [e]Department of Life Science, Graduate Institute of Applied Science and Engineering, College of Science and Engineering, Fu Jen Catholic University, Taipei, Taiwan; [f]Department of Pathology, Cardinal Tien Hospital, Medical School, Fu Jen Catholic University, New Taipei City, Taiwan

Correspondence: Yen-Lin Chen · Department of Pathology, Cardinal Tien Hospital, No 362, Chung Cheng Road, Xindian, Taipei County 23137, Taiwan · T: +886-2-22193391 F: +886-2-22195821 · anthonypatho@gmail.com

BACKGROUND: Type 2 diabetes mellitus (T2DM) is characterized by impaired insulin sensitivity (Si) and insulin secretion. Previous studies may have underestimated differences in the incidence of risk factors in insulin-sensitive diabetes mellitus (IS-DM) and insultin-resistant diabetes mellitus (IR-DM) patients and have not been conducted in the Chinese population.

OBJECTIVES: We explored differences in metabolic risk factors between Chinese patients with newly diagnosed, insulin-resistant (IR) and insulin-sensitive (IS) T2DM.

DESIGN: Cross-sectional study.

SETTING: Cardinal Tien Hospital, Taiwan in 2011.

METHODS: All participants received a frequently sampled intravenous glucose tolerance test. The acute insulin response after a glucose load (AIRg), Si, disposition index (DI), and glucose effectiveness (GE) were determined. Using the median Si value from 90 people without diabetes as a cutoff (1.19×10^{-4} mU/L/min), patients were divided into two groups, IS-DM and IR-DM. Multivariate regression analysis was used to examine the independent influence of MetS components on Si and AIRg.

MAIN OUTCOME MEASURE(S): Insulin sensitivity.

RESULTS: We enrolled 122 participants. In addition to higher probabilities of having MetS, IR-DM patients had a significantly higher body mass index (BMI), AIRg, and GE but a lower DI than IS-DM patients. Si correlated with BMI and triglycerides, and AIRg correlated with BMI and high-density lipoprotein cholesterol. BMI was the only component related to Si in the multivariate analysis. Furthermore, the AIRg was associated with BMI and fasting plasma glucose. Because BMI was the most critical factor, a cutoff value (25.0 kg/m^2) was obtained from the receiver operating characteristic curve for predicting IR-DM. It showed a sensitivity and specificity of 60.8% and 60.9%, respectively.

CONCLUSIONS: IR-DM patients had more MetS components than IS-DM patients. In Chinese patients obesity is the most critical factor for discriminating IR-DM from IS-DM. Patients with a BMI higher than 25 kg/m^2 were prone to develop IR-DM.

LIMITATIONS: The size of our study cohort was relatively small, which may weaken the statistical power of the study.

Although patients with type 2 diabetes mellitus (T2DM) present with hyperglycemia, it is generally agreed that T2DM is heterogeneous and is composed of different underlying defects in glucose homeostasis. At present, the most commonly recognized pathophysiologies of T2DM are increased insulin resistance (IR) and decreased insulin secretion.[1] Insulin sensitivity (Si), which is conceptually reciprocal to IR, has

been shown to deteriorate in youth in people prone to develop diabetes. This defect is compensated for by increased insulin secretion to maintain glucose balance. Eventually, after years of compensation, β-cells enter a stage of decompensation. Subsequently, clinically overt diabetes is diagnosed on the basis of an elevated fasting plasma glucose (FPG) level. Because it is one of the key factors inducing diabetes, it is logical to postulate that IR should be found exclusively in diabetic patients. However, the degree of IR varies not only among people with normal glucose tolerance[2] but also among those with T2DM.[3,4] Moreover, some patients with T2DM have been considered insulin sensitive (IS).[4,5] These findings indicate that at least two subtypes of T2DM may exist, IS- and IR-DM. In these two subtypes, IR and increased insulin secretion might differ in relative importance in either triggering the occurrence of T2DM or maintaining fair glucose control after diabetes is diagnosed.[5]

In addition to its role in causing diabetes, IR has been found to be the core manifestation of metabolic syndrome (MetS), which is the clustering of glucose intolerance, dyslipidemia, obesity, and hypertension.[6,7] In addition, individual MetS components, including waist circumference (WC), blood pressure, fasting triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and FPG, have been shown to be correlated with IR.[8,11] Thus, it is unsurprising that patients with MetS have a higher risk of T2DM and cardiovascular disease (CVD) than that of patients without MetS.[12] This close relationship between MetS and CVD was also observed in T2DM.[13] As mentioned, IR varies among T2DM patients; thus, we hypothesize that differences should be observed in the incidence of MetS and other CVD risk factors between IS-DM and IR-DM patients. This hypothesis has been proven by Haffner et al. In 1999, they compared individual MetS risk factors between IS-DM and IR-DM patients and demonstrated that IR-DM patients had higher WC, HDL-C, and FPG but lower TG values than IS-DM patients in the Insulin Resistance Atherosclerosis Study (IRAS).[4] However, more than 40% of their patients with T2DM were not drug naïve, potentially leading to underestimation of the results. Moreover, because Chinese people are less obese than Caucasians, and metabolic risks differ between the Chinese ethnicity and other ethnicities,[14,15] it is imperative to explore differences between IR- and IS-DM in the Chinese population. Hence, in the present study, we investigated differences between the two subtypes of T2DM, IR- and IS-DM, by analyzing metabolic risk factors in patients with newly diagnosed T2DM. Moreover, we constructed models to predict IR- and IS-DM on the basis of these metabolic risk factors.

PATIENTS AND METHODS

Patients
We enrolled patients with newly diagnosed T2DM from our outpatient clinic in 2011 (12 months); their age ranged from 24 to 79 years. These patients were either self-referred or referred by other health professionals while seeking to be screened for diabetes. They had no other notable medical diseases or history of diabetic ketoacidosis, and they had not taken any medications with known effects on IR or β-cell function during the study period. The diagnostic criteria for T2DM were based on the 2012 American Diabetes Association recommendation.[16] On the day of the study, a complete routine work-up was performed to exclude the presence of cardiovascular, endocrine, renal, hepatic, and respiratory disorders. BMI was calculated as body weight/height (kg/m²), and systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured on the right arm of seated patients by using a standard mercury sphygmomanometer. Two measurements were taken at 10-minute intervals. The mean of these two measurements was used in analysis. Blood samples were drawn from the antecubital vein for biochemical analysis. In this study, MetS was defined using the criteria proposed by the National Cholesterol Education Program, Adult Treatment Panel III.[17] The definitions include the following: plasma TG ≥1.7 mmol/L, SBP ≥130 mm Hg or DBP ≥85 mm Hg, plasma HDL-C <0.9 mmol/L in men or <1.0 in women, and BMI ≥27 kg/m². It should be noted that we used BMI instead of WC, because WC was not measured in this study. The cutoff value used for obesity was based on the value proposed by the Taiwanese Department of Health. Because all patients had T2DM, those meeting any two of these four criteria were regarded as fulfilling the diagnosis of MetS.

Because there is no established cutoff value for defining IS- and IR-DM, we followed the method used by Haffner et al.[4] In brief, the median Si value derived from a frequently sampled intravenous glucose tolerance test (FSIGT) and minimal model in a cohort with normal glucose tolerance was defined as the cutoff value. Hence, we enrolled 90 subjects without diabetes and found that the median Si value was $1.19×10^4$ mU/L/min. Patients with Si higher and lower than this value were classified into the IS-DM and IR-DM groups, respectively. The study protocol was approved by the hospital's institutional review board and ethics committee, and all patients provided written informed consent before participation.

Protocols

Each participant received an FSIGT, and the test was performed at 0800 with patients in the sitting position after a 10-hour overnight fast. An intravenous catheter was placed in each forearm; one catheter was used for blood sampling and the second was used for glucose infusion. The sampling catheters were kept patent by slow infusion of 0.9% saline.

After placement of the catheters, a bolus of 10% glucose water (0.3 g/kg) was administered. Another bolus of regular human insulin (0.05 units/kg; Novo Nordisk Pharmaceutical, Princeton) was injected 20 minutes after the glucose load. Blood samples were collected at 0, 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 minutes for measuring plasma glucose and insulin levels. The data were input into Bergman's minimal model, and SI, glucose effectiveness (GE), and the acute insulin response after the glucose load (AIRg) were then determined. The AIRg was used to measure β-cell function in the present study.[18] The disposition index (DI) is the product of Si and the AIRg, which is the estimate of IR-adjusted insulin secretion. GE is the rate of glucose metabolism independent of insulin action. Patients with higher SI, AIRgDI and GE values were considered to have greater glucose metabolism even though they were diabetic.

Laboratory measurements

The blood samples were centrifuged immediately and stored at -30°C until the time of analysis. Plasma insulin levels were measured using a commercial solid-phase radioimmunoassay kit (Coat-A-Count Insulin Kit, Diagnostic Products Corporation, Los Angeles, CA, USA). Intra- and interassay coefficients of variance for insulin were 3.3% and 2.5%, respectively. Plasma glucose levels were measured using the glucose oxidase method (YSI 203 glucose analyzer, Scientific Division, Yellow Spring Instrument Company Inc., Yellow Spring, OH, USA). Serum total cholesterol (TC), TG, and HDL-C were measured using the Fuji DRI-Chem 3000 analyzer by employing the dry, multilayer analytical slide method (Fuji Photo Film Corporation Minato-Ku Tokyo, Japan).

Statistical analysis

Statistical analysis was performed using SPSS for Windows software (Version 10.0; SPSS, Chicago, IL). The data were tested for normal distribution by the Kolmogorov–Smirnov test and for the homogeneity of variances by the Levene test. Because fasting plasma insulin (FPI), the AIRg, and the DI showed a right-skewed distribution, a log transformation was performed before analysis. The data are presented as the mean and standard deviation. An independent t test was used to compare the demographic data, clinical characteristics, and parameters derived from the FSIGT between the two groups. The χ^2 test was used to examine relationships between the categorical data of the two subtypes of diabetes. Pearson correlation was performed to assess relationships between MetS components and either Si or AIRg. The stepwise multiple linear regression method was used to examine the influence of the confounding variables. MetS components were used as independent variables and SI, AIRg, DI, or GE as the dependent variable.

The predictive performance of the variables for IR-DM was first evaluated using logistic regression. The receiver operating characteristic (ROC) curve of each variable (or model) was then plotted as sensitivity (true-positive rate, y-axis) against 1–specificity (false-positive rate, x-axis). The area under the ROC curve was calculated using the trapezoidal rule, which was then used to determine the predictive accuracy of the models. In general, a larger area corresponds to a higher predictive accuracy for a variable (model).[19] The variables with significant *P* values were used to construct models with more than one MetS component. Thus, the accuracy of prediction could be increased. Finally, the optimal cutoff values with the highest sensitivity and specificity were selected. These cutoff values could be used in routine clinical practice.

All statistical tests were two-sided, and a *P* value <.05 was considered significant.

RESULTS

We enrolled 122 participants with ages ranging from 24 to 79 years. IR-DM patients had significantly higher BMI, AIRg, and GE but lower DI values than those of IS-DM patients (**Table 1**). However, no significant difference was observed in age, gender, BP, lipid profile, FPG, and FPI between the two groups. Si was correlated with BMI and TG, and the AIRg was correlated with BMI and HDL-C (**Table 2**). In addition, the DI was negatively associated with HDL-C, and no significant association was observed between GE and other MetS components. In the multiple linear regression, Si was independently related to BMI, and the AIRg was associated with both BMI and FPG (**Table 3**). The patients in the IR-DM group had a significantly higher number of MetS components than did those in the IS-DM group (2.8 [1.3] vs. 2.3 [0.9]) (**Figure 1A**). The patients in the IR-DM group had a significantly higher percentage of MetS components than their counterparts (57.4% and 38.1%, respectively) (**Figure 1B**).

Table 1. Demographic data and parameters derived from the frequently sampled intravenous glucose tolerance test for insulin-resistant and insulin-sensitive subtypes of type 2 diabetes mellitus.

Variables	IS-DM	IR-DM	P
Number of patients (male/female)	71 (40:31)	51 (26:25)	.558
Age (years) Fasting plasma glucose (mmol/L)	51.2 (11.8) 10.1 (2.3)	53.4 (10.1) 9.5 (1.9)	.283 .125
Body mass index (kg/m²)	24.4 (3.0)	26.5 (4.1)	.002
Systolic blood pressure (mmHg)	121.3 (14.0)	124.2 (14.7)	.289
Diastolic blood pressure (mmHg)	76.5 (7.6)	76.5 (9.0)	.910
Triglycerides (mmol/L)	1.4 (0.6)	1.5 (0.6)	.118
High-density lipoprotein (mmol/L)	1.1 (0.3)	1.2 (0.3)	.203
Log FPI (pmol/L)	1.4 (0.5)	1.5 (0.7)	.330
Log AIRg (mU/min)	1.5 (0.7)	1.8 (0.8)	.023
Insulin sensitivity (10−4 mU/L/min)	3.0 (1.6)	0.4 (0.4)	.000
Log disposition index	1.9 (0.7)	1.4 (0.8)	.003
Glucose effectiveness (min−1)	0.013 (0.008)	0.016 (0.009)	.024

Data are presented as the mean ± standard deviation; IS-DM: insulin-sensitive type 2 diabetes mellitus; IR-DM: insulin-resistant type 2 diabetes mellitus; FPI: fasting plasma insulin; AIRg: acute insulin response after a glucose load.

Table 2. Pearson correlations of metabolic syndrome components with insulin sensitivity and the acute insulin response after glucose load in patients with type 2 diabetes mellitus.

Variables	Si (P value)	Log AIRg (P value)	Log DI (P value)	GE (P value)
BMI	−0.237 (.009)	0.286 (.006)	0.091 (.409)	0.007 (.942)
SBP	−0.049 (.597)	0.032 (.762)	−0.024 (.825)	0.028 (.767)
DBP	−0.008 (.932)	0.033 (.765)	−0.046 (.688)	0.099 (.302)
TG	−0.201 (.028)	0.182 (.086)	0.046 (.678)	−0.098 (.288)
HDL-C	0.112 (.230)	−0.240 (.023)	−0.034 (.005)	0.020 (.829)
FPG	−0.033 (.717)	−0.191 (.067)	−0.055 (.614)	−0.006 (.950)

Si: insulin sensitivity; AIRg: acute insulin response after a glucose load; DI: disposition index; GE: glucose effectiveness; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; FPG: fasting plasma glucose.

Table 3. Multiple linear regression of metabolic syndrome components with insulin sensitivity and acute insulin response after a glucose load.

Variables	Log Si Beta (P value)	Log AIRg Beta (P value)
BMI	−0.188 (.049)	0.339 (.001)
TG	−0.121 (.204)	-
HDL-C	-	−0.193 (.057)
FPG	-	−0.227 (.027)

Beta, standardized coefficient; Si: insulin sensitivity; AIRg: acute insulin response after a glucose load; BMI: body mass index; SBP: systolic blood pressure; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; FPG: fasting plasma glucose.
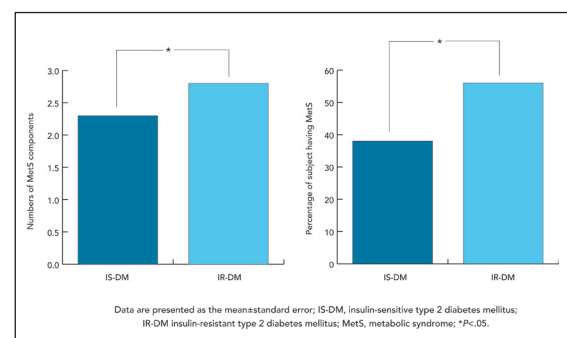

Data are presented as the mean±standard error; IS-DM, insulin-sensitive type 2 diabetes mellitus; IR-DM insulin-resistant type 2 diabetes mellitus; MetS, metabolic syndrome; *P<.05.

Figure 1. Numbers of metabolic syndrome components (A) and percentage of patients having metabolic syndrome (B) in insulin-sensitive and insulin-resistant type 2 diabetes mellitus groups.
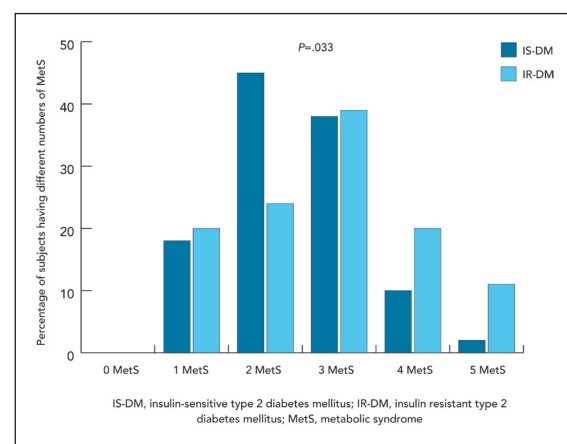

IS-DM, insulin-sensitive type 2 diabetes mellitus; IR-DM, insulin resistant type 2 diabetes mellitus; MetS, metabolic syndrome

Figure 2. Percentage of the subjects having different numbers of metabolic syndrome components in insulin-sensitive and insulin-resistant type 2 diabetes mellitus groups.

The different numbers of MetS components in these two groups are shown in **Figure 2**. The trend in the IS-DM group obviously shifts to the left, with a significantly higher percentage of patients having two MetS components compared with the IR-DM group. To determine the reason for this difference, each MetS component was separately studied (**Figure 3**). Although higher percentages of patients met the criteria for abnormal BP, BMI, and TG in the IR-DM group than in the IS-DM group, only the percentage of patients with a high BMI reached significance.

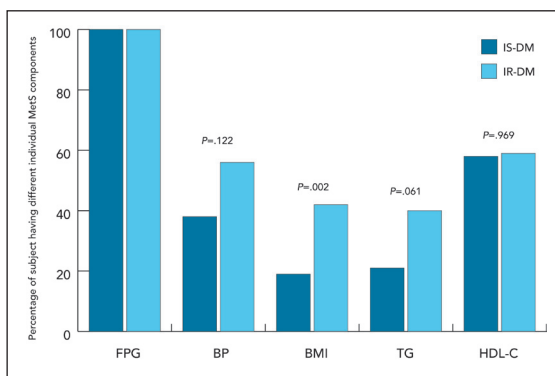Because BMI is the major contributor to differences

Figure 3. Percentage of the subjects having different individual metabolic syndrome components in insulin-sensitive and insulin-resistant type 2 diabetes mellitus groups.
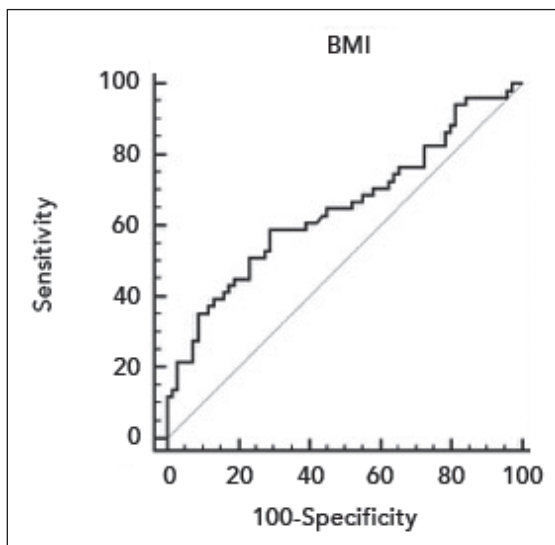

Figure 4. Area under the receiver operating characteristic curve of body mass index (BMI). The arrow indicates the arbitrarily selected risk score cutoff (25.0 kg/m²) of BMI, which has a sensitivity and specificity of 60.8% and 60.9 respectively.

between the IS-DM and IR-DM groups, we used BMI as a predictor to differentiate between IS-DM and IR-DM. From the cutoff value of BMI obtained from the ROC curve (**Figure 4**) we found that patients with a BMI higher than 25.0 kg/m² were classified into the IR-DM group. The sensitivity and specificity were 60.8% and 60.9%, respectively. Furthermore, we applied the cutoff value of obesity to our Chinese patients to divide them into obese (BMI ≥27 kg/m²) and nonobese (BMI <27 kg/m²) groups. The specificity improved to 84%; however, the sensitivity decreased to 41% (**Table 4**).

DISCUSSION

The present study is the second study to investigate the difference in clinical characteristics between IS-DM and IR-DM. The first study was conducted by Haffner et al in 1999. However, compared with that study, the present study had three unique findings: first, all participants were drug naïve; second, only Chinese patients were studied; and finally, in addition to IS and the AIRg, we examined the DI and GE in these two groups. Because clinical characteristics differ between Caucasian and Chinese ethnicities, we believe that the results of our study could provide essential information for further understanding the pathophysiology of diabetes.[14,15]

The AIRg, SI, DI, and GE are critical factors controlling the occurrence of diabetes. In our study, the IR-DM group had a higher AIRg than that of the IS-DM group, which is consistent with the result of Haffner et al.[4] This could be attributed to two causes. The first is that a higher BMI, which is associated with greater insulin secretion, was found in the IR-DM group.[20] Alternatively, the higher IR found in the IR-DM group could drive β-cells to secrete more insulin. In addition to a higher AIRg, higher GE was observed in the IR-DM group than in the IS-DM group. Furthermore, the range of GE in IR-DM patients was similar to that in nondiabetic people. This finding is unexpected because it is generally agreed that GE is lower in patients with more severe glucose intolerance.[21] Nevertheless,

Table 4. Comparison of obese and nonobese patients with insulin-sensitive and insulin-resistant type 2 diabetes mellitus.

	IS-DM	**IR-DM**
Non-obese	58	29
Obese	13	22

P=.005, nonobese: BMI <27 kg/m², obese: BMI ≥27 kg/m². IS-DM: insulin-sensitive type 2 diabetes mellitus; IR-DM: insulin-resistant type 2 diabetes mellitus; Sensitivity: 41.0%; specificity: 84.0%; positive predictive value: 71.4%; negative predictive value: 58.6%

our result is not unique because a similar finding was reported by Garcia-Estevez et al.[5] All of this evidence clearly suggests that along with increased AIRg, GE is another critical factor in IR-DM that compensates for the decrease in SI.[5] Thus, we hypothesize that despite compensation by AIRg and GE, the decrease in Si is severe to the extent that the diabetic condition persists in patients with IR-DM.

Finally, the DI is the product of the AIRg and SI, and very few studies have focused on its importance. In our study, contrary to the AIRg, the patients in the IR-DM group had a lower DI, which is in agreement with the results of Chung et al.[22] This finding could only be explained by the possibility that the effect of the higher AIRg is surpassed by the more severe decrease in SI. Under this circumstance, the product of these two factors (i.e., DI) could then be lower in the IR-DM group. This observation of the change in DI is basically compatible with our discussion in the preceding paragraph.

Compared with the IRAS, several interesting differences were observed in our study. First, in the IRAS, the IR-DM group had higher WC, BMI, FPG, and TG but lower HDL-C values. However, in our study, we found that only BMI was higher in the IR-DM group. This particularly critical role of BMI indicates that all MetS components are likely to be related to BMI in the Chinese population. In other words, BMI is the core of both MetS and diabetes in the Chinese, but not Caucasian, ethnicity. Thus, in the present study, we established 25 kg/m^2 as the cutoff value on the basis of BMI. Patients with a BMI higher than this value were classified into the IR-DM group, with a sensitivity of 60.8% and a specificity of 60.9%. Second, BMI was higher in the IRAS (27.1-31.7 vs. 24.4-26.5 kg/m^2) than in our study. This is expected because the average BMI in Caucasians with T2DM is higher than that in Chinese patients with T2DM. Because BMI is positively related to IR, this increased adiposity contributes to not only higher IR but also a higher incidence of MetS.[23] Finally, patients in the IRAS were older compared with the participants in our study (57.0-58.6, 52.3 years, respectively). Because aging strongly affects IR, older age could have led to further deterioration of Si in patients in the IRAS, resulting in divergences between the two studies. All of these aforementioned differences should be considered when applying the results in clinical practice.

Table 2 shows that in addition to BMI, TG was negatively related to SI. All correlations of Si with HDL-C, SBP, DBP, and FPG were non-significant. However, when evaluated by dividing study participants into the IR- and IS-DM groups, the difference in TG became non-significant (**Table 1** and **Figure 3**). Furthermore, after BMI and TG were both entered into multiple linear regression model to examine whether TG was independently related to SI, the relationship became non-significant again (**Table 3**). All of these findings indicate that differences in TG between the IR- and IS-DM groups, if any, are secondary to BMI in Chinese patients. Additional studies with a larger cohort are required to validate the inference.

Although our data are novel and informative, some limitations still exist. First, WC, an index of central obesity and IR, was not measured in this study. However, evidence has shown that the correlation between BMI and WC is high.[15] Thus, we still consider our results reliable. Second, because we did not collect information on exercise and smoking, we were unable to analyze their effects on SI. Because all study participants were diabetic, the influence of smoking and exercise should be less compared with the influence in healthy people. Finally, the size of our study cohort was relatively small, and as previously discussed, IR differs with ethnicity. Therefore, using the same definition as that used in the IRAS to identify IS-DM and IR-DM in our study may not be appropriate.

In conclusion, in newly diagnosed, drug-naïve Chinese patients with T2DM, those in the IR-DM group had significantly more abnormal MetS components than those in the IS-DM group did. Unlike in Caucasians, in Chinese patients, obesity is the single most critical factor used to discriminate IR-DM from IS-DM. Chinese patients with a BMI higher than 25 kg/m^2 were prone to develop IR-DM. Our results support that fact that T2DM may have two subtypes.

REFERENCES

1. DeFronzo RA, Abdul-Ghani MA. Preservation of beta-cell function: the key to diabetes prevention. J Clin Endocrinol Metab 2011;96:2354-66.

2. Lin JD, Chang JB, Wu CZ, Pei D, Hsieh CH, Hsieh AT, Chen YL, Hsu CH, Liu CC. Identification of insulin resistance in subjects with normal glucose tolerance. Ann Acad Med Singapore 2014;43:113-9.

3. Haffner SM, Howard G, Mayer E, Bergman RN, Savage PJ, Rewers M, Mykkanen L, Karter AJ, Hamman R, Saad MF. Insulin sensitivity and acute insulin response in African-Americans, non-Hispanic whites, and Hispanics with NIDDM: the Insulin Resistance Atherosclerosis Study. Diabetes 1997;46:63-9.

4. Haffner SM, D'Agostino R, Jr., Mykkanen L, Tracy R, Howard B, Rewers M, Selby J, Savage PJ, Saad MF. Insulin sensitivity in subjects with type 2 diabetes. Relationship to cardiovascular risk factors: the Insulin Resistance Atherosclerosis Study. Diabetes Care 1999;22:562-8.

5. Garcia-Estevez DA, Araujo-Vilar D, Saavedra-Gonzalez A, Fiestras-Janeiro G, Cabezas-Cerrato J. Glucose metabolism in lean patients with mild type 2 diabetes mellitus: evidence for insulin-sensitive and insulin-resistant variants. Metabolism 2002;51:1047-52.

6. Salazar MR, Carbajal HA, Espeche WG, Dulbecco CA, Aizpurua M, Marillet AG, Echeverria RF, Reaven GM. Relationships among insulin resistance, obesity, diagnosis of the metabolic syndrome and cardio-metabolic risk. Diab Vasc Dis Res 2011;8:109-16.

7. Reaven GM. Is diagnosing metabolic syndrome a uniquely simple way to predict incident type 2 diabetes mellitus? CMAJ 2009;180:601-2.

8. Flowers E, Molina C, Mathur A, Reaven GM. Use of plasma triglyceride/high-density lipoprotein cholesterol ratio to identify increased cardio-metabolic risk in young, healthy South Asians. Indian J Med Res 2015;141:68-74.

9. Hanley AJ, Williams K, Gonzalez C, D'Agostino RB, Jr., Wagenknecht LE, Stern MP, Haffner SM. Prediction of type 2 diabetes using simple measures of insulin resistance: combined results from the San Antonio Heart Study, the Mexico City Diabetes Study, and the Insulin Resistance Atherosclerosis Study. Diabetes 2003;52:463-9.

10. Cheal KL, Abbasi F, Lamendola C, McLaughlin T, Reaven GM, Ford ES. Relationship to insulin resistance of the adult treatment panel III diagnostic criteria for identification of the metabolic syndrome. Diabetes 2004;53:1195-200.

11. Lin JD, Chen YL, Hsu CH, Wu CZ, Hsieh CH, Chang JB, Liang YJ, Pei D. Beta-cell function and insulin sensitivity at various degrees of glucose tolerance in Chinese subjects. Diabetes Res Clin Pract 2013;100:391-7.

12. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005;365:1415-28.

13. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 2005;112:3066-72.

14. Torrens JI, Skurnick J, Davidow AL, Korenman SG, Santoro N, Soto-Greene M, Lasser N, Weiss G. Ethnic differences in insulin sensitivity and beta-cell function in premenopausal or early perimenopausal women without diabetes: the Study of Women's Health Across the Nation (SWAN). Diabetes Care 2004;27:354-61.

15. Ko GT, Chan JC, Cockram CS, Woo J. Prediction of hypertension, diabetes, dyslipidaemia or albuminuria using simple anthropometric indexes in Hong Kong Chinese. Int J Obes Relat Metab Disord 1999;23:1136-42.

16. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2012;35 Suppl 1:S1-2.

17. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Jama 2001;285:2486-97.

18. Bergman RN, Ader M, Huecking K, Van Citters G. Accurate assessment of beta-cell function: the hyperbolic correction. Diabetes 2002;51 Suppl 1:S212-20.

19. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148:839-43.

20. Kloppel G, Lohr M, Habich K, Oberholzer M, Heitz PU. Islet pathology and the pathogenesis of type 1 and type 2 diabetes mellitus revisited. Survey and Synthesis of Pathology Research 1985;4:110-25.

21. Best JD, Kahn SE, Ader M, Watanabe RM, Ni TC, Bergman RN. Role of glucose effectiveness in the determination of glucose tolerance. Diabetes Care 1996;19:1018-30.

22. Chung JO, Cho DH, Chung DJ, Chung MY. Associations among body mass index, insulin resistance, and pancreatic beta-cell function in Korean patients with new-onset type 2 diabetes. Korean J Intern Med 2012;27:66-71.

23. Vega GL. Results of Expert Meetings: Obesity and Cardiovascular Disease. Obesity, the metabolic syndrome, and cardiovascular disease. Am Heart J 2001;142:1108-16.