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Diagnosis of Insulin Resistance in Hypertensive Patients by the Metabolic Syndrome: AHA vs. IDF Definitions

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SUMMARY

Background—Subjects with the metabolic syndrome are accompanied by insulin resistance (IR). However, it is not clear how well the newly-defined metabolic syndrome identifying IR specifically in hypertensive subjects.

Aims—The purpose of the study is to evaluate the performance of the metabolic syndrome, defined by the American Heart Association (AHA) and the International Diabetes Federation (IDF) definitions, in identifying IR in hypertension.

Methods—The analysis is a cross-sectional study. Totally, 228 hypertensive patients and 92 non-diabetic normotensive controls who received insulin suppressive tests to directly evaluate their insulin sensitivity were included from the Stanford Asia and Pacific Program for Hypertension and IR. McNemar's tests were used to compare sensitivity and specificity of the AHA-defined with the IDF-defined metabolic syndrome in diagnosis of IR.

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Results—The sensitivity of the metabolic syndrome for IR in hypertension was 89.7 % and the specificity 45.9 % by the AHA definition. Using the IDF definition, the sensitivity was 77.6 %, and the specificity increased to 63.5 %. The diagnostic power of individual components of the syndrome was also modest. The predictive discrimination of wider waist circumference was similar to that of the AHA-defined metabolic syndrome.

Conclusions—Use of the metabolic syndrome by the AHA definition provided good sensitivity but low specificity to diagnose IR in hypertension. The IDF definition improved in false positive rate, but it was still not specific enough to identify IR in hypertension.

Keywords

hypertension; insulin resistance; metabolic syndrome; steady-state plasma glucose

What's known?

Hypertensive patients with insulin resistance are at greater risk of cardiovascular disease. Few studies have evaluated the performance of the metabolic syndrome defined by the new definitions for insulin resistance in subjects with hypertension.

What's new?

Use of the metabolic syndrome by the AHA definition provided good sensitivity but low specificity to diagnose insulin resistance in hypertension. The IDF definition improved in false positive rate, but it was still not specific enough to identify insulin resistance in hypertension.

Introduction

Insulin resistance (IR) has been proposed to be a key feature linked to hypertension-related metabolic disorders (1). Evidence shows that hypertensive patients with IR are at greater risk of cardiovascular disease and may represent a particular subset of hypertension that requires special medical attention (2). Several attempts have been made to measure IR in hypertension quantitatively including glucose clamp methods and insulin suppression tests (IST) (3). However, these techniques are complicated and generally not suitable for routine clinical work. Surrogate estimates of insulin sensitivity in hypertension have been published (4). It was suggested that insulin sensitivity indices integrating post-challenge values surrogated insulin sensitivity in hypertension better than those that used fasting measures alone (4). When oral glucose tolerance test (OGTT) is not available, simple clinical markers are options to clinicians for the diagnosis of IR in hypertension.

Karter *et al.* demonstrated that waist circumference (WC) was significantly associated with IR (5). McLaughlin *et al.* proposed that triglyceride (TG) level, ratio of TG to high-density lipoprotein cholesterol (HDL-C), and insulin level were the most useful common laboratory tests for identifying subjects who had IR (6). The metabolic syndrome is a constellation of risk factors of metabolic origin. It is generally believed that subjects with the metabolic syndrome are accompanied by IR (7). The correspondence between the metabolic syndrome and IR has been evaluated in earlier studies (8-10). Although IR and the presence of the metabolic syndrome were significantly associated (8), the metabolic syndrome defined by the Adult Treatment Panel III (ATP III) criteria did not provide a sensitive approach to identifying insulin-resistant individuals (8-10). Recently, the American Heart Association (AHA) along with the National Heart, Lung and Blood Institute issued an up-to-date version on the diagnosis of the metabolic syndrome (11). The International Diabetes Federation (IDF) also provided a working definition for the syndrome (12). Few studies have evaluated

the performance of the metabolic syndrome defined by the new definitions for IR in subjects with hypertension. The purpose of this study is to assess how well these new definitions identify directly-measured IR in hypertensive subjects from the Stanford Asia and Pacific Program for Hypertension and IR (SAPPHIRE). Moreover, we are interested in examining whether the newly-defined metabolic syndrome diagnoses IR better than the components of the syndrome in subjects with hypertension.

Methods

Subjects

The study is a part of the SAPPHIRE. The study population has been reported previously (13). In the present analysis, 228 (119 men, 109 women) Taiwanese hypertensive patients who received IST to evaluate *in vivo* insulin sensitivity were included. The hypertensive patients were between 35 and 60 years old and without other health problems. All participants with known diabetes and fasting plasma glucose (PG) ≥ 7.0 mmol/L were excluded from the study. Another 92 non-diabetes (2-h glucose < 7.8 mmol/L) subjects without hypertension from Taiwan were included as controls. The Institutional Review Board from each center approved the study and each participant gave written informed consent before entering the study. Clinical examination and measurements

The participants received anthropometric measurements at 8 AM after 10 hours overnight fast. Body mass index (BMI) (kg/m^2) was calculated from body weight (BW) and body height (BH). WC was measured at the level of umbilicus. Sitting blood pressure (BP) was measured by an automated oscillometric BP recorder (Dinamap 1864SX, Critikon, Tampa, FL). Each subject was subjected to a 75-g OGTT thereafter for fasting samples and 2-h glucose and insulin. On a separate visit, within 3-7 days of the first visit, the participants underwent an IST to assess insulin sensitivity after a 10-h overnight fasting by procedures reported earlier (13). The subjects were asked to refrain from strenuous exercise 3 days before the tests. They were suggested to keep their regular diet pattern, not to avoid carbohydrate intakes before the tests. No alcohol was allowed in the 3 days preceding the tests. Smoking and chewing gum were prohibited at the fasting period and during the tests. All subjects were infused with regular insulin (Humulin-R, Lilly, Indiana, USA; 25 mU/ $\text{min}\cdot\text{m}^2$) and glucose (TAIYU, Shin-Tzu, Taiwan; 240 mg/ $\text{min}\cdot\text{m}^2$) simultaneously for 180 minutes with infusion pumps (Harvard Apparatus, Boston, MA, USA). In addition, somatostatin (5 $\mu\text{g}/\text{min}$) (Somatostan, Ferring, Switzerland) was infused intravenously over the same period of time. The mean values of PG at 150, 160, 170 and 180 minutes during the IST were defined as SSPG that represented *in vivo* insulin sensitivity of the subjects.

PG was measured by a glucose oxidase method in a glucose analyzer (Elan Diagnostics, Smithfield, RI). Plasma insulin was measured by an enzymatic immunoassay (Access system, Beckman Coulter, Fullerton, CA). Lipid profile including total cholesterol (TC), total triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) was measured by previously described methods (13).

Statistical analysis

Logarithmic transformation (Log) was applied to subordinate the skewness of 2-h glucose and TG values. Continuous data were expressed as mean $\pm$ S.D. The mean values of glucose at the last 30-min during IST were defined as steady-state plasma glucose (SSPG). One-way analysis of variance (ANOVA) with *post hoc* Duncan tests was applied to compare the differences among the groups. The diagnosis criteria of the metabolic syndrome used in the study are shown in Table 1. We basically followed the AHA (11) and the IDF (12) definitions with ethnic-specific values for WC cutoffs (men ≥ 90 cm and women ≥ 80 cm

for Chinese). The sensitivity and specificity of the metabolic syndrome and its components for the diagnosis of IR were calculated. McNemar's test was used to compare sensitivities and specificities between markers (14). A p value < 0.05 was considered to be significant.

Results

A total of 320 subjects (228 hypertensives and 92 controls) were included in the study. Among them, 5 were using anti-lipid agents. There were 99 hypertensive subjects in the study using β -blockers, 21 with diuretics, and 7 using both β -blockers and diuretics. However, due to ethical reasons we could not discontinue the use of anti-hypertensive and lipid-lowering agents in our participants. The clinical characteristics of the participants are shown in Table 2. The (mean + 2 SD) SSPG value in the control group (i.e. 13.7 mmol/L) was chosen as the cut-point for IR, following the suggestions from Lind *et al* (15). Among the hypertensive patients, 25 of them were undiagnosed diabetes (i.e. 2h PG ≥ 11.1 mmol/L), 75 impaired glucose tolerance ($7.8 \leq 2h\text{ PG} < 11.1$ mmol/L) and 128 non-diabetes (2h PG < 7.8 mmol/L). The hypertensive subjects with IR were more obese and with larger girth than the non-insulin-resistant (non-IR) hypertensives. Their fasting and 2-h PG levels and fasting TG were also higher than the controls and the non-IR hypertensives.

The sensitivity and specificity of clinical markers for IR in hypertension were listed in Table 3. The sensitivity and specificity of the metabolic syndrome by the AHA criteria (11) on IR in subjects with hypertension were 89.7 % and 45.9 % respectively. Using the IDF definitions (12), the sensitivity was 77.6 % and the specificity 63.5 %. The AHA definition had a high sensitivity and a high false positive rate (i.e. 1-specificity) (54.1 % vs. 36.5 %) in comparison with the IDF definition. If large WC (men ≥ 90 cm, women ≥ 80 cm) was used for cut-offs, the sensitivity was 86.2 % and the specificity was 49.4 %. Using TG ≥ 1.7 mmol/L as a cut-point, we could diagnose IR with 48.3 % sensitivity and 67.7 % specificity in hypertensive subjects. The predictive discrimination of the AHA-defined metabolic syndrome was similar to that of wider WC.

Discussion

In the present study, we want to detect hypertensive patients with IR by simple clinical markers and routine laboratory measurements, but without using the OGTT. The diagnosis of the metabolic syndrome in the study is to serve as a clinical marker for IR. Our data suggest that the many faces of the metabolic syndrome actually produce substantial outlooks of the syndrome in prediction of IR. Although both the AHA and the IDF definitions carry the same medical term of the metabolic syndrome, they are different clinical tools for the diagnosis of IR in hypertension.

We found in the study that the updates of the metabolic syndrome provided good sensitivity (around 80 %) but low-to-moderate specificity (50-60 %) for screening IR in hypertensive patients. Liao *et al.* (9) and other investigators (10) reported earlier that the metabolic syndrome by the ATP III criteria had low sensitivity around 50 % and high specificity more than 90 % for the diagnosis of IR. The revisions of the metabolic syndrome, especially in lowering the threshold for impaired glucose from 6.1 to 5.6 mmol/L, improved sensitivity for identifying subjects with impaired glucose tolerance (16), and probably having impacts on the diagnostic power of the syndrome for IR.

Sierra-Johnson *et al.* suggested earlier that use of additional measures beyond WC by the ATP III criteria for metabolic syndrome did not add value to either sensitivity or specificity in the identification of insulin-resistant individuals (10). Our results also demonstrated that the correspondence between the AHA-defined metabolic syndrome and IR was similar to

the application of just measuring WC alone (Table 3). The AHA revision of the metabolic syndrome does not improve much in term of diagnosing IR than the ATP-III version when the components of the metabolic syndrome were considered.

With the requiring that there should be abdominal obesity for the metabolic syndrome, the IDF definition further reduced false positive rate for about 18 % than the AHA definition at the expense of sensitivity. Although the IDF-defined metabolic syndrome had a better specificity, the specificity was nevertheless less than satisfaction in identifying subjects with both hypertension and IR. Refinement of the metabolic syndrome such as using TG/HDL-C ratio (6) or reducing TG cut-offs from 1.7 mmol/L to 1.6 mmol/L for men and 1.4 mmol/L for women (17) is recently suggested. More studies are needed to improve the diagnostic power of the metabolic syndrome for IR.

It has been demonstrated in the Insulin Resistance Atherosclerosis Study that more than 90 % of diabetic patients were insulin resistant (18). In the Belfast Diet Study, Levy *et al.* reported that there was no change in IR during a 10-year follow-up of a group of newly diagnosed type 2 diabetes (19). Therefore, the diagnosis of diabetes itself represents a good marker of IR. In clinical practice we can use medical history and fasting glucose levels ≥ 7 mmol/L to identify those with frank diabetes and to label them with IR. However, those with silent diabetes (fasting glucose < 7 mmol/L but 2h glucose ≥ 11.1 mmol/L) and impaired glucose tolerance (IGT) can not be easily identified by clinical markers unless using OGTT. It has been reported that more than 25 % of the hypertensive patients were either IGT or silent diabetes (20). These subjects and those with isolated IR (i.e., only with IR but without abnormalities in fasting and/or 2-h PG) constitute a major body of IR in hypertension. And, this is why we did not exclude those subjects with silent diabetes and IGT in the study.

There are limitations to our study. The cut-off value of SSPG for IR was arbitrary. We followed the suggestions by Lind *et al.* (15) to define a cutoff limit for IR as the (mean + 2 SD) SSPG value in the control group. At this cutoff limit, 25.4 % of the hypertensive subjects were insulin resistant. A similar prevalence (27 %) of IR in hypertensive patients was also found in Lind's study by euglycemic clamp methods (15). By the cutoff, the hypertensive subjects labeling with IR in this study not only displayed a higher degree of obesity, PG and TG levels as compared with the controls but also showed discrepancy from the non-IR counterparts (Table 2). Since sensitivity and specificity of a diagnostic test are not fixed, they will change with different spectrum of the subjects. We are very cautious in extrapolation of the results into other studies when different attempts are made to define IR. Second, many hypertensive patients also have diabetes. We excluded all known diabetic subjects and those with fasting PG ≥ 7.0 mmol/L in the study because of the study design. The prevalence of IR among hypertensive patients would probably higher in a study in which diabetic hypertension was included, resulting in different sensitivity and specificity for IR by the metabolic syndrome. Another limit was the concomitant use of antihypertensive agents such as β -blockers and diuretics in many of the study subjects. While in an earlier study we have found that hypertensive patients who were taking β -blockers and/or diuretics showed no difference in insulin sensitivity in the SAPHIRE as compared with those not taking these agents (21), this is clearly an important consideration to take into account when the results are applied to naïve patients.

On the measurements of insulin sensitivity, although the IST satisfactorily measures IR directly, it suffers from some practical drawbacks including cost, variable reproducibility, urinary glucose loss, and inability to distinguish between hepatic and peripheral insulin sensitivity. And, there is no cardiovascular outcome study for IST as a measure of IR (3). On the surrogates of IR, we do not consider using fasting insulin as an estimate of IR in hypertension. There is a lack of standardization of insulin assays. Insulin is not routinely

measured in clinical practice. Above all, Stern *et al.* have developed decision-tree models to identify individuals with IR. Their results showed that the models did not include insulin measurements were only slightly less accurate (~ 5 %) than the model included insulin (22). It seems that measurements of fasting insulin do not add values to a model with simple clinical markers and routine laboratory measurements for predicting IR.

In a 13-year follow-up, Bigazzi *et al.* reported that hypertensive patients with IR, measured directly by the clamps, were at greater risk in the development of cardiovascular disease than those without IR (23). Moreover, Meigs *et al.* from the Framingham Offspring Study demonstrated that the simultaneous presence of the metabolic syndrome and IR represented an especially high-risk group for diabetes and cardiovascular disease (24). Although it is a challenge to catch information of directly-measured IR by common clinical markers, the IDF definition of the metabolic syndrome improved in specificity and with a fair sensitivity for the diagnosis of IR in hypertension. Even so, fine tuning of the syndrome is essential for a better application in clinical diagnosis of IR.

In conclusion, using the IDF definition of the metabolic syndrome to diagnose IR in hypertension is better than using the AHA definition. The predictive discrimination of the AHA-defined metabolic syndrome was similar to that of wider WC.

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Table 1

The diagnosis of the metabolic syndrome in the study

Components	Definitions of the Metabolic Syndrome	
	AHA ¹	IDF ²
WC (cm)		(A must)
Chinese men	≥ 90 cm	≥ 90 cm
Chinese Women	≥ 80 cm	≥ 80 cm
TG (mmol/L), or	≥ 1.7	≥ 1.7
on lipid-lowering agents	Yes	Yes
HDL-C (mmol/L)		
Men	< 1.0	< 1.0
Women	< 1.3	< 1.3
or on lipid-lowering agents	Yes	Yes
BP (mmHg)		
Systolic BP, or	≥ 130	≥ 130
Diastolic BP, or	≥ 85	≥ 85
Hypertension	Yes	Yes
Fasting PG (mmol/L)	≥ 5.6	≥ 5.6

AHA = American Heart Association; IDF = International Diabetes Federation; WC = waist circumference; TG = total triglycerides; HDL-C = high-density-lipoprotein cholesterol; BP = blood pressure; HT = hypertension; PG = plasma glucose.

¹ Three or more out of the five components are required for the diagnosis of the metabolic syndrome in subjects without hypertension. For subjects with hypertension, additional two or more out of the four components (WC, TG, HDL-C and fasting PG) are required.

² The component of abdominal obesity is a must for the IDF definition plus any two or more of the remaining components for non-hypertensive subjects. For hypertensive patients, in addition to abdominal obesity and hypertension, they still need to have at least one more component for the diagnosis of the metabolic syndrome.

Table 2

A comparison of clinical characteristics in study subjects from the SAPHIRE with or without insulin resistance

	HT		Non-DM, Non-HT
	IR ¹ (n = 58)	Non-IR (n = 170)	Control ² (n = 92)
Sex (male/female)	28/30	91/79	31/61
Age (years)	50.0 ± 8.4 ^c	49.8 ± 7.4 ^b	45.7 ± 7.5 ^{***}
BH (cm)	162.3 ± 7.5	161.9 ± 8.3	160.9 ± 7.5
BW (kg)	73.8 ± 10.5 ^{ac}	68.0 ± 11.4 ^b	60.4 ± 9.3 ^{***}
BMI (kg/m ²)	28.0 ± 3.3 ^{ac}	25.8 ± 3.2 ^b	23.3 ± 2.9 ^{***}
WC (cm)	91.2 ± 7.7	86.2 ± 9.9	77.9 ± 9.0
Fasting PG (mmol/L)	5.6 ± 0.6 ^{ac}	4.9 ± 0.6	4.8 ± 0.5 ^{***}
Log (2-h PG)	2.22 ± 0.14 ^{ac}	2.09 ± 0.13 ^b	2.02 ± 0.08 ^{***}
Log TG	2.15 ± 0.21 ^{ac}	2.07 ± 0.22 ^b	1.94 ± 0.24 ^{***}
TC (mmol/L)	4.9 ± 1.0	4.9 ± 1.1	4.6 ± 1.1
HDL-C (mmol/L)	1.0 ± 0.2 ^c	1.1 ± 0.3 ^b	1.2 ± 0.4 ^{**}
Systolic BP (mmHg)	136 ± 22 ^c	141 ± 23 ^b	106 ± 10 ^{***}
Diastolic BP (mmHg)	80 ± 11 ^{ac}	83 ± 13 ^b	66 ± 7.3 ^{***}
SSPG (mmol/L)	15.3 ± 1.4 ^{ac}	9.3 ± 2.9 ^b	7.1 ± 3.3 ^{***}
Metabolic syndrome (%) (AHA)	52 (89.7 %)	92 (54.1 %)	4 (4.4 %) ^{***}
Metabolic syndrome (%) (IDF)	45 (77.6 %)	62 (36.5 %)	2 (2.2 %) ^{***}

HT = hypertension; DM = diabetes; BH = body height; BW = body weight; BMI = body mass index; WC = waist circumference; PG = plasma glucose; 2-h PG = 2-hour post-loading plasma glucose; Log (2h PG) = log transformation of 2-h PG in mg/dL; TG = total triglycerides; Log TG = log transformation of TG in mg/dL; TC = total cholesterol; HDL-C = high-density-lipoprotein cholesterol; BP = blood pressure; SSPG = steady-state plasma glucose; AHA = American Heart Association; IDF = International Diabetes Federation.

Data are expressed as mean ± SD or n (%).

¹IR, insulin resistant = those with SSPG values ≥ (Mean + 2 SD) of SSPG from the non-DM non-HT control. Non-IR = those with hypertension but not with SSPG in the range of insulin resistance.

²Non-DM, non HT controls = non-hypertensive subjects with 2-h glucose < 7.8 mmol/L

**
 $p < 0.01$,

 $p < 0.0001$ by ANOVA or χ^2 tests

^aMultiple comparison: non-IR vs. IR;

^bnon-IR vs. Control;

^cIR vs. Control.

Table 3

Sensitivity and specificity of various clinical markers for the diagnosis of insulin resistance in the hypertensive subjects from the SAPPHiRe

	Hypertensive (n = 228)			
	Sensitivity (%)	<i>p</i> ¹	Specificity (%)	<i>p</i> ¹
WC (men ≥ 90 cm; women ≥ 80 cm)	86.2	0.41	49.4	0.29
TG (≥ 1.7 mmol/L)	48.3	< 0.0001	67.7	< 0.0001
FPG (≥ 5.6 mmol/L)	50.0	< 0.0001	85.3	< 0.0001
Metabolic syndrome (AHA)	89.7	-	45.9	-
Metabolic syndrome (IDF)	77.6	0.008	63.5	< 0.0001

AHA = American Heart Association; IDF = International Diabetes Federation; WC = waist circumference; TG = total triglycerides; HDL-C = high-density-lipoprotein cholesterol; BP = blood pressure; HT = hypertension; PG = plasma glucose.

¹ McNemar's test was used to compare sensitivities and specificities between markers using the AHA-defined metabolic syndrome as reference.