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Utility of elevated 2-hour postload plasma glucose as an alternative to elevated fasting glucose as a criterion for the metabolic syndrome

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Abstract

We hypothesize that many persons with postchallenge hyperglycemia (PCH) but who do not meet the National Cholesterol Education Program (NCEP) criteria characterize a phenotype that is similar to the metabolic syndrome (MS) traits. Subjects included 725 Japanese who underwent a 75-g oral glucose tolerance test. If 2-hour plasma glucose of 7.8 mmol/L or higher was present, subjects with fasting glucose of less than 6.1 mmol/L could have one component of the MS (PCH-MS). Data obtained by the 75-g oral glucose tolerance test were used to calculate 3 insulin sensitivity indexes according to formulas proposed by Matsuda and DeFronzo (insulin sensitivity index composite), Stumvoll et al (Srumvoll index), and Mari et al (oral glucose insulin sensitivity index). Based on the PCH-MS and NCEP-MS criteria, 395 had neither PCH-MS nor NCEP-MS, 85 had PCH-MS, and 245 had NCEP-MS. Subjects with PCH-MS exhibited higher systolic blood pressure and triglyceride levels, lower high-density lipoprotein cholesterol levels, and lower insulin sensitivity than those who had neither PCH-MS nor NCEP-MS. A similar profile was observed when subjects with NCEP-MS were compared with those who had neither PCH-MS nor NCEP-MS. All 3 indexes of insulin sensitivity were significantly lower in subjects with PCH-MS than in those who had neither PCH-MS nor NCEP-MS, and approximately 66% of PCH-MS was in an insulin-resistant state. On the other hand, there was no statistical difference in the values between PCH-MS and NCEP-MS. Our data support the addition of abnormal 2-hour plasma glucose as a criterion for the MS, when fasting glucose is normal.

1. Introduction

The diagnostic criteria of the metabolic syndrome (MS) proposed by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [1] are currently the most widely used, because it can be easily applied to the primary care setting. The report recommended the use of 5 variables for diagnosis of the MS: high fasting glucose levels, high blood pressure, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol levels, and central obesity. On the basis of this definition, however, it may fail to identify many persons with postchallenge hyperglycemia (PCH) among individuals who did not meet the MS according to the standard NCEP criteria. Impaired glucose tolerance (IGT) and impaired fasting glucose may represent different phenotypes, and several investigators found that fasting plasma glucose (FPG) is less predictive of cardiovascular incidence than PCH [2,3]. It seems likely that persons with PCH but with normal FPG levels characterize a phenotype that is similar to the MS traits [4]. The aim of this study was to evaluate the utility of PCH in addition to fasting hyperglycemia for determinants of the MS traits in Japanese subjects who are not very obese.

2. Methods

2.1. Subjects

The study population was selected from 924 subjects who underwent a 75-g oral glucose tolerance test (OGTT) as part of an evaluation for glucose intolerance to determine whether they have one or more of the following risk factors: are overweight (body mass index [BMI], ≥ 25 kg/m^2), have a first-degree relative with diabetes, and have a past history of gestational diabetes mellitus, hypertension, dyslipidemia, or vascular disease [5]. Exclusion criteria were incomplete

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Table 1
Clinical and metabolic characteristics of subjects classified by MS status

Variables	Neither	PCH-MS	NCEP-MS	*P*, trend
n	395	85	245	
Age (y)	63.48 ± 0.56	63.35 ± 1.21	59.46 ± 0.71**,†	<.001
Female (%)	28.4	27.1	41.2**,†	.002
BMI (kg/m^2)	22.72 ± 0.15	24.90 ± 0.33**	26.69 ± 0.19**,†	<.001
BMI >30 (%)	2.0	8.2	11.4**	<.001
Abdominal obesity (%)	18.2	58.8**	86.9**,††	<.001
SBP (mm Hg)	127.7 ± 1.0	134.9 ± 2.1**	138.8 ± 1.2**	<.001
DBP (mm Hg)	72.2 ± 0.01	75.5 ± 1.3	79.5 ± 0.8**,†	<.001
Fasting glucose (mmol/L)	5.36 ± 0.04	5.34 ± 0.09	5.98 ± 0.05**,††	<.001
2-h glucose (mmol/L)	8.04 ± 0.14	10.01 ± 0.29**	10.66 ± 0.17**	<.001
Fasting insulin (pmol/L)	35.96 ± 1.19	44.25 ± 2.56*	52.02 ± 1.51**,†	<.001
2-h insulin (pmol/L)	302.6 ± 12.7	462.5 ± 27.4**	427.5 ± 16.1**	<.001
Total cholesterol (mmol/L)	5.19 ± 0.06	5.05 ± 0.12	5.45 ± 0.07*,†	.003
Triglycerides (mmol/L)	1.23 ± 0.04	1.49 ± 0.09*	2.12 ± 0.05**,††	<.001
HDL-C (mmol/L)	1.39 ± 0.02	1.24 ± 0.04**	1.10 ± 0.03**,†	<.001

Data are mean ± SE or %.
SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol.
* $P < .05$ vs subjects who had neither PCH-MS nor NCEP-MS.
** $P < .01$ vs subjects who had neither PCH-MS nor NCEP-MS.
† $P < .05$ vs PCH-MS.
†† $P < .01$ vs PCH-MS.

data collection for evaluating the MS components; incomplete data for calculating the insulin sensitivity index; or those with signs of serious liver diseases, chronic infectious diseases, renal failure, endocrine diseases which affect insulin secretion or insulin sensitivity, cancer, or those with a prior gastrectomy. Finally, a total of 725 subjects were included in the present analysis. This study was performed in accordance with the Helsinki Declaration, and written informed consent was obtained from each participant.

2.2. Oral glucose tolerance test

A 75-g OGTT was performed after a 10-hour overnight fast. Plasma glucose was determined using a glucose oxidase autoanalyzer, and plasma insulin was measured using an electrochemiluminescence immunoassay (Roche-Diagnostic, Basel, Switzerland), which does not cross-react with pro-insulin.

2.3. Definition of the MS

Metabolic syndrome was defined according to the NCEP ATP III [1], as modified for waist circumference criteria by the Regional Office for the Western Pacific Region of the World Health Organization [6]. Based on this modified definition, subjects were defined as having the MS (NCEP-MS) if they have 3 or more of the following 5 components: abdominal adiposity (waist circumference of ≥90 cm in men and ≥80 cm in women), high blood pressure (≥130 mm Hg systolic or ≥85 mm Hg diastolic or current use of antihypertensive medication), hypertriglyceridemia (≥1.7 mmol/L), low HDL cholesterol (<1.0 mmol/L in men and <1.3 mmol/L in women), and high fasting glucose level (≥6.1 mmol/L). We also analyzed the contribution of the OGTT values to the MS. If 2-hour plasma glucose (PG) of 7.8 mmol/L or higher was present, subjects with FPG of less than 6.1 mmol/L could have one component of the MS instead of fasting glucose criteria. An alternative diagnosis of the MS (PCH-MS) requires "2-hour PG of 7.8 mmol/L or higher" in combination with 2 of the other 4 components.

2.4. Evaluation for insulin sensitivity

Data obtained by the 75-g OGTT were used to calculate 3 insulin sensitivity indexes according to 3 formulas: insulin sensitivity index composite by Matsuda and DeFronzo [7] (ISI-COMP), insulin sensitivity index by Stumvoll et al [8] (Stumvoll index), respectively, and oral glucose insulin sensitivity index by Mari [9] (OGIS index).

Table 2
Insulin sensitivity of subjects classified by MS status

	Neither	PCH-MS	NCEP-MS	*P*, trend
ISI-COMP	21.48 ± 0.51	16.34 ± 1.10*	14.17 ± 0.65*	<.001
IR%[a]	14.2%	28.2%*	41.2%*,†	<.001
Stumvoll index ($\times 10^{-3}$)	99.6 ± 1.2	75.6 ± 2.5*	68.7 ± 1.5*	<.001
IR%[a]	9.6%	32.9%*	46.9%*,††	<.001
OGIS index	454.2 ± 4.8	367.3 ± 10.3*	357.8 ± 6.1*	<.001
IR%[a]	24.3%	62.4%*	67.3%*	<.001
Insulin resistance[b]	32.7%	65.9%*	76.7%*,††	<.001

Data are mean ± SE or %. IR indicates insulin resistance.
[a] Insulin resistance was diagnosed as each parameter being below the lowest quartile.
[b] Insulin resistance was diagnosed as any one of the 3 parameters being below the lowest quartile.
* $P < .01$ vs subjects who had neither PCH-MS nor NCEP-MS.
† $P < .05$ vs PCH-MS.
†† $P < .01$ vs PCH-MS.

Table 3
Spearman correlation analysis of associations of ISI-COMP, Stumvoll index, and OGIS index with the MS variables

	ISI-COMP	Stumvoll index	OGIS index
Waist circumference	−0.401***	−0.657***	−0.410***
SBP	−0.112**	−0.150**	−0.076*
DBP	−0.094*	−0.119**	−0.040
Triglycerides	−0.168***	−0.228***	−0.161***
HDL cholesterol	0.219***	0.261***	0.179***
Fasting glucose	−0.268***	−0.315***	−0.564***
2-h glucose	−0.176***	−0.533***	−0.789***

* $P < .05$.
** $P < .01$.
*** $P < .001$.

These mathematical indexes are accurate and valid techniques for the measurement of insulin sensitivity even in relatively lean Japanese [10,11]. Insulin resistance was defined as the lowest quartile of each parameter in the nondiabetic population.

2.5. Statistical analysis

All statistical analyses were performed using the SYSTAT statistical package (Systat Software, Inc, Point Richmond, CA). When the subjects were divided into 3 groups (without MS, PCH-MS, and NCEP-MS), the difference among 3 groups was tested using analysis of variance with post hoc test. The association of ISI-COMP, Stumvoll index, and OGIS index with variables used in the MS definitions was assessed using Spearman correlation analysis. A P value of less than .05 was considered to be statistically significant.

3. Results

The characteristics of the study subjects subdivided on the basis of their status with or without the MS are listed in Table 1. Of the 725 subjects, 395 (54.5%) had neither PCH-MS nor NCEP-MS, 85 (11.7%) had PCH-MS, and 245 (33.8%) had NCEP-MS. There was a linear increase in BMI across the 3 groups. The prevalence of subjects with obesity (BMI, $\geq$30 kg/m^2) was somewhat low in the 3 groups (2.0%, 8.2%, and 11.4%, respectively). Subjects with PCH-MS exhibited higher systolic blood pressure, higher triglyceride levels, and lower HDL cholesterol levels than subjects who had neither PCH-MS nor NCEP-MS. Similar trends were observed when subjects with NCEP-MS were compared with subjects who had neither PCH-MS nor NCEP-MS. In the NCEP-MS group, triglyceride levels were significantly higher and HDL-cholesterol levels were significantly lower than in the PCH-MS group.

Table 2 represents the insulin sensitivity indexes of the study population by MS status. All 3 indexes were significantly lower in subjects with PCH-MS than in those who had neither PCH-MS nor NCEP-MS, and approximately 66% of subjects with PCH-MS were in an insulin-resistant state. On the other hand, there was no statistical difference in the values between PCH-MS and NCEP-MS.

Various measures of insulin sensitivity were inversely correlated with the majority of MS components, including waist circumference, systolic and diastolic blood pressure, triglyceride level, and fasting glucose level; and had a positive correlation with HDL cholesterol levels (Table 3). Especially, ISI-COMP showed moderate but significant inverse association with waist circumference. Oral glucose insulin sensitivity index showed moderate inverse correlation with waist circumference and strong inverse correlations with fasting and 2-hour PG. Stumvoll index also showed strong inverse correlations with waist circumference and 2-hour PG.

4. Discussion

Several diagnostic approaches have been proposed to distinguish the high-risk persons who have an adverse cardiovascular disease risk profile [12]. Insulin resistance and IGT are closely associated with cardiovascular disease and may originate from a common physiologic antecedent. It is generally believed that insulin resistance is the common pathogenic factor for the MS. However, few studies have examined the associations between NCEP-MS and direct measure of insulin resistance [4,13]. Liao et al [4] reported that approximately one third of subjects who did not meet NCEP-MS were insulin resistant, as measured by hyperinsulinemic-euglycemic clamp. Hanley et al [13] also reported that only 32% of subjects with NCEP-MS were insulin resistant, which was determined using the frequently sampled intravenous glucose tolerance test. These studies suggest that the associations between insulin resistance and the MS are notably weaker using the NCEP definition. Importantly, metabolic abnormalities may differ among ethnic groups [14] and Japanese subjects are lean relative to other ethnic groups. To our knowledge, the present study provides the first information on insulin sensitivity in relatively lean Japanese subjects with or without NCEP-MS. In our data, approximately 77% of subjects with NCEP-MS had insulin resistance. Furthermore, 66% of subjects with PCH-MS had insulin resistance. Our data have also shown comparable levels of insulin sensitivity between PCH-MS and NCEP-MS. These findings support the importance of 2-hour postload PG in evaluating the MS. In the Framingham Offspring Study, Meigs et al [15] reported that PCH is an independent risk factor for cardiovascular disease. But approximately 30% to 60% of subjects with IGT have normal fasting glucose levels, so fasting testing alone does not detect the many subjects at risk for cardiovascular disease. These findings have important clinical and public health implications because PCH-MS is thought to be a risk for future cardiovascular disease. It seems that there is a clear improvement in risk prediction when using the NCEP criteria in combination with additional 2-hour PG levels.

There are a number of limitations in the present study. First, assessment of abdominal adiposity must be ethnically based. In Asian populations, specific cutoff points for BMI

and waist circumference should be considered [16]. A review of Asian data concluded that Asians had a higher percentage of body fat at a lower BMI than whites [17]. Recently, the Regional Office for the Western Pacific Region of the World Health Organization proposed a separate classification for abdominal adiposity in Asia [6]. We used this cutoff point for waist girth ($\geq$90 cm in men and $\geq$80 cm in women) [6] because the cutoff points used by the original criteria of NCEP ATP III (>102 cm in men and >88 cm in women) may not be applicable to Asians. Indeed, the prevalence of obesity higher than 30 kg/m^2 in BMI was relatively low in our subjects. It seems likely that a Japanese individual with the MS does not indicate obvious obesity. Secondly, the validity of surrogate indices of insulin sensitivity must be considered. The euglycemic-hyperinsulinemic clamp is a standard method for the measurement of insulin sensitivity, but its invasiveness and high cost have limited its use in clinical practice. To date, clinical researches have chosen the homeostasis model assessment ratio (HOMA-R) as a surrogate measure of insulin resistance [18]. But it seems likely that HOMA-R is influenced by the degree of compensatory hyperinsulinemia and hepatic insulin resistance. Notably, Japanese are lean relative to whites and fasting hyperinsulinemia is not common even in subjects with the MS. Indeed, in the present study, average fasting insulin in the NCEP-MS group was 52.0 pmol/L (not exceeding 60 pmol/L). In this sense, Mari et al [19] compared surrogate insulin sensitivity methods based on the OGTT and demonstrated that OGIS and Stumvoll index had clear advantages over HOMA-R. Then, we used 3 surrogate indexes of insulin sensitivity based on the OGTT results in the present study. We have previously shown that those indexes were valid markers of insulin resistance for relatively lean Japanese [10,11]. Using the surrogate markers, we confirmed that insulin resistance is increased even in subjects with PCH-MS as well as in those with NCEP-MS. Finally, in the present study, approximately 34% of study subjects fulfilled the NCEP criteria for the MS. The prevalence was considerably higher than the 7.9% to 19.5% reported in the unselected sample [20]. This was not surprising considering the very high prevalence because, by study design, we focused on subjects from the selected high-risk population.

In conclusion, insulin resistance and the MS frequently coexist in relatively lean Japanese population. We believe that the NCEP definition, when applied relatively to lean Japanese, may underestimate the prevalence of insulin resistance phenotypes and suggest the need to introduce the NCEP criteria in combination with additional 2-hour PG levels in assessing the MS traits.

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