Quantitative Insulin Sensitivity Check Index Is a Useful Indicator of Insulin Resistance in Japanese Metabolically Obese, Normal-Weight Subjects with Normal Glucose Tolerance

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Abstract. To clarify whether quantitative insulin sensitivity check index (QUICKI) is useful as an indicator of insulin resistance in Japanese metabolically obese, normal-weight (MONW, body mass index (BMI) <25 and visceral fat area (VFA) ≥100 cm² by abdominal computed tomography scanning) subjects with normal glucose tolerance (NGT). Insulin resistance was measured by QUICKI and euglycemic hyperinsulinemic clamp study (clamp IR) in 27 MONW and 27 normal subjects (BMI <25 and visceral fat area <100 cm²). QUICKI (P<0.01) and clamp IR (p<0.01) were significantly decreased in MONW subjects compared with normal subjects. QUICKI was significantly associated with VFA [MONW subjects: r = –0.459, p<0.02; all (MONW and normal) subjects: r = –0.506, p<0.0001] and with the serum levels of triglycerides (MONW subjects: r = –0.386, p<0.05; all subjects: r = –0.505, p<0.001) in MONW and all subjects. There were significant correlations between clamp IR and VFA (MONW subjects: r = –0.562, p<0.01; all subjects: r = –0.575, p<0.0001), fasting serum levels of insulin (MONW subjects: r = –0.673, p<0.001; all subjects: r = –0.619, p<0.0001) or serum levels of triglycerides (MONW subjects: r = –0.485, p<0.02; all subjects: r = –0.565, p<0.0001) in MONW and all subjects. QUICKI was significantly correlated with clamp IR in MONW (r = 0.754, p<0.0001) and in all subjects (r = 0.568, p<0.0001). QUICKI may be an useful method for assessing insulin resistance in Japanese MONW subjects with NGT.

Key words: Insulin resistance, QUICKI, Metabolic obesity, Normal glucose tolerance

SEDENTARY life and increment of western diet have caused an increase in the number of obese subjects in Japan [1–4]. Recently, we described the existence of metabolically obese, normal-weight (MONW) subjects [body mass index (BMI) <25 kg/m² and visceral fat area (VFA) evaluated by abdominal computed tomography (CT) scanning ≥100 cm²] in the Japanese population, and demonstrated that insulin resistance and visceral fat accumulation play an important role in the pathophysiology of metabolic obesity [5–10]. To prevent or retard the development of atherosclerosis, early identification of MONW subjects with normal glucose tolerance (NGT) during a general health check-up examination is fundamental. In addition to visceral fat, insulin resistance is also necessary for the diagnosis of...
MONW subjects [5–8]. However, a simple and accurate index of insulin resistance in Japanese MONW subjects with NGT has not been as yet to be established.

Quantitative insulin sensitivity check index (QUICKI) has been reported to be better than insulin resistance index by homeostasis model assessment (HOMA IR) as a marker of insulin resistance under different conditions [11, 12]. QUICKI has been found to be particularly suitable for epidemiological surveys [13–17]. However, its usefulness in Japanese MONW subjects with NGT has not been studied as yet.

In the present study, we investigated whether QUICKI correlates with the index of euglycemic hyperinsulinemic clamp study (clamp IR) in Japanese MONW subjects with NGT.

**Subjects and Methods**

**Subjects**

This study comprised 27 MONW and 27 normal subjects (BMI <25 kg/m$^2$ and VFA <100 cm$^2$) (Table 1). BMI was calculated as the body weight (in kilograms) divided by the square of the height (in meters).

None of the subjects had impaired glucose tolerance (IGT) or diabetes mellitus according to the diagnostic criteria of the American Diabetes Association (ADA) based on the 75-g oral glucose tolerance test (OGTT) (Trelan G 75, Shimizu, Shimizu, Japan) [18]. None of the subjects had past history of obesity. Five MONW subjects had family history of diabetes mellitus or obesity among their first-degree relatives. Three normal subjects had family history of diabetes mellitus or obesity among their first-degree relatives. Eleven MONW subjects had hyperlipidemia (total cholesterol ≥5.7 mmol/l or TG ≥1.7 mmol/l) and two with hypertension (blood pressure ≥140/90 mmHg). None of the normal subjects had hyperlipidemia or hypertension.

Informed consent was obtained from all subjects before the beginning of the study.

**Methods**

Body fat area was evaluated by a previously described method [19]. At 8 a.m., after an overnight fast of 11 hours, all subjects underwent single abdominal computed tomography (CT) scanning at the umbilical level. Any intraperitoneal region having the same density as the subcutaneous fat layer was defined as a VFA; this area was measured by tracing object contours on films using a computerized planimetric method.

The plasma glucose level was measured by an automated enzymatic method. Serum insulin was measured using an immunoradiometric assay kit (Insulin Ria bead II kit, Dainabot, Tokyo, Japan). The intra- and inter-assay coefficients of variation of the assay were 2.0% and 2.1%, respectively. No significant cross-reactivity or interference was observed between insulin and proinsulin, C-peptide, glucagon, secretin or gastrin-I. Serum levels of total cholesterol, triglycerides, and HDL cholesterol were measured by enzymatic methods using an autoanalyzer (TBA60M, Toshiba, Tokyo, Japan).

QUICKI was calculated from the fasting concentrations of insulin and glucose using the following formula: $\text{QUICKI} = 1/[\log \text{fasting serum insulin (µU/ml)} + \log \text{fasting plasma glucose (mg/dl)}]$ [11]. Clamp IR was evaluated by the euglycemic hyperinsulinemic clamp technique using an artificial pancreas (STG-22, Nikkiso, Tokyo, Japan) [20]. At 8 a.m., a priming dose of insulin (Humulin R, Eli Lilly Japan, Kobe, Japan) was administered during the initial 10 min in a logarithmically decreasing manner to rapidly raise serum insulin to the desired level (1200 pmol/l); this level was then maintained by continuous infusion of insulin at a rate of 13.44 pmol/kg/min for 120 min. The mean insulin level from 90 to 120 min after starting the clamp study was stable (MONW subjects: 1380.0 ± 426.0 pmol/l; Normal subjects: 1339.8 ± 371.4 pmol/l). Blood
glucose was monitored continuously and it was maintained at the target clamp level (5.24 mmol/l) by infusing 10% glucose. The mean amount of glucose given during the last 30 min was defined as the glucose infusion rate (GIR), and this was considered as the clamp IR.

Statistical analysis

Data were expressed as the means ± SD. Differences between MONW and normal subjects were determined by unpaired t tests. Correlations between variables were evaluated by univariate regression analysis. Unpaired t tests and correlations were carried out using the StatView 5.0 software program (Abacus Concepts, Berkeley, CA) for the Macintosh. A p<0.05 was considered as statistically significant.

Results

Fasting serum levels of insulin (p<0.01) and triglycerides (p<0.01) and the systolic (p<0.01) and diastolic (p<0.01) blood pressure were significantly increased in MONW subjects compared to normal subjects (Table 1). The clamp IR (p<0.01) and QUICKI (p<0.01) were significantly decreased in MONW subjects compared to normal subjects (Table 1). The value of HOMA IR [HOMA IR = fasting serum insulin (µU/ml) × fasting plasma glucose (mmol/l)/22.5] were also calculated. HOMA IR in MONW subjects (1.9 ± 1.0) was significantly increased compared to normal subjects (1.0 ± 0.4, p<0.01).

QUICKI was significantly correlated with VFA (MONW subjects: r = –0.459, p<0.02; all subjects: r = –0.506, p<0.0001) and with the serum levels of triglycerides (MONW subjects: r = –0.386, p<0.05; all subjects: r = –0.505, p<0.001) in MONW and in all subjects.

Clamp IR was significantly correlated with VFA (MONW subjects: r = –0.562, p<0.01; all subjects: r = –0.575, p<0.0001) and with the fasting serum levels of insulin (MONW subjects: r = –0.673, p<0.001; all subjects: r = –0.619, p<0.0001) and triglycerides (MONW subjects: r = –0.485, p<0.02; all subjects: r = –0.565, p<0.0001) in MONW and in all subjects.

QUICKI was significantly correlated with clamp IR in MONW (r = 0.754, p<0.0001) (Fig. 1) and in all subjects (r = 0.568, p<0.0001). There was no significant correlation between QUICKI and clamp IR in normal subjects (r = 0.278, p = 0.16).

Log-transformed HOMA IR was significantly correlated with clamp IR in MONW (r = –0.742, p<0.0001) and in all subjects (r = –0.607, p<0.0001).

Discussion

This is the first report that demonstrates the usefulness of QUICKI in Japanese MONW subjects with NGT.

Insulin resistance, hyperinsulinemia and hypertriglyceridemia in association with visceral adiposity have been reported in Japanese MONW subjects with NGT, suggesting the need of early diagnosis and intervention in these subjects [8–10]. However, in surveys of obesity as defined by BMI, MONW subjects are generally categorized as normal individuals. Evaluation of visceral fat by waist circumference, and insulin resistance by QUICKI may be useful for early diagnosis and intervention to prevent the development of atherosclerosis in MONW subjects with NGT [1]. However, before the routine use of QUICKI in general health check-up, firstly it is necessary to define the normal values of QUICKI. For this purpose, we measured QUICKI in 189 normal subjects (male/female, 30/159; age, 50.3 ± 7.0 years old; BMI, 21.6 ± 1.9, <25; waist circumference, male 77.4 ± 5.0 cm, <85 cm;
female, 69.2 ± 5.5 cm, <90 cm; total cholesterol, 4.9 ± 0.5 mmol/l, <5.7 mmol/l; TG, 0.9 ± 0.3 mmol/l, <1.7 mmol/l; blood pressure, 117.1 ± 11.4/72.4 ± 8.8 mmHg, <140/90 mmHg), and found that the mean value of QUICKI in healthy subjects was 0.389 ± 0.054 (mean ± 2SD). However, further studies in a larger population should be carried out to more accurately define the normal value of QUICKI.

The degree of adiposity has been reported to affect the relationship between QUICKI and clamp IR [13, 21]. The correlation coefficient between QUICKI and clamp IR is high in obese and type 2 diabetic patients but relatively low in lean non-diabetic subjects. The characteristics of MONW subjects are similar to obese individuals, particularly to subjects with abdominal obesity. The explanation for the correlation of QUICKI with clamp IR is unclear but it may depend on the close relationship between the degree of lipolysis in adipose tissue and the flux of free fatty acids from adipocytes to the liver [22]. Visceral fat accumulation may play an important role in the interaction between peripheral lipolysis and hepatic glucose output.

Many studies have reported the usefulness of QUICKI in type 2 diabetic patients [11, 13–15]. Yokoyama et al. demonstrated the usefulness of QUICKI in type 2 diabetic patients with wide range of fasting plasma glucose [16]. We previously demonstrated that QUICKI cannot predict insulin resistance in older patients with poorly controlled type 2 diabetes mellitus [23]. The usefulness of QUICKI in type 2 diabetic patients according to aging and the fasting plasma levels of glucose needs to be clarified in future investigations.

On the other hand Katz et al. reported that the correlation between QUICKI and clamp is significantly better than that between HOMA IR and clamp IR in normal, obese and diabetic subjects [11]. Previous studies have shown that both QUICKI and HOMA IR are good alternative indices of insulin resistance in healthy and diabetic subjects [15, 16]. In agreement with this, the present study demonstrated that both QUICKI and HOMA IR are significantly correlated with clamp IR in MONW subjects with NGT. Comparative evaluation between QUICKI and HOMA IR is also necessary in a larger population and under different conditions.

In conclusion, the results of this study showed that QUICKI may be useful for screening and early diagnosis of insulin resistance in Japanese MONW subjects with NGT.

References


