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Correlation of body muscle/fat ratio with insulin sensitivity using hyperinsulinemic-euglycemic clamp in treatment-naïve type 2 diabetes mellitus

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ABSTRACT

Aims: Fat deposition and obesity are crucial pathological components of diabetes mellitus (DM). In clinical practice, assessment of insulin resistance is important. We hypothesized that body muscle and fat composition might be a key factor for insulin resistance in patients with type 2 DM.

Methods: Subjects included 61 untreated DM patients. Hyperinsulinemic-euglycemic clamp examination was performed to calculate the M/I value as the insulin resistance reference indicator. Elementary body composition was measured by impedance analysis using InBody770.

Results: Simple regression analysis showed that total muscle quantity/total fat quantity ratio (muscle/fat) was significantly correlated with M/I value ($B = 0.806$, $P < 0.001$). The regression equation was M/I value = 3.6934 × (muscle/fat ratio) + 0.0347 ($R^2 = 0.6503$, $P < 0.001$). Multivariate logistic regression analysis showed that muscle/fat ratio was independently and significantly associated with insulin resistance, defined by M/I value <9 (odds ratio, 0.89; 95% confidence interval, 0.80–0.99, $P = 0.04$). With receiver operating curve analysis, the cutoff value of muscle/fat ratio for insulin resistance was 2.40 and area under the curve was 0.87 (sensitivity 91% and specificity 76%, $P < 0.001$), indicating that muscle/fat ratio was significantly effective for predicting insulin resistance in treatment-naïve DM. The result could provide a possible estimation of the M/I value using the regression equation M/I value = 2.5438 × (muscle/fat ratio) + 48.6194 × QUICKI − 13.6522 ($R^2 = 0.7012$).

Conclusion: In treatment-naïve DM, the muscle/fat ratio, assessed by InBody770 is clinically useful for evaluating the presence of insulin resistance in daily clinical practice.

1. Introduction

Obesity and fat deposition are closely involved in the pathogenesis of diabetes mellitus (DM) because of their effect on insulin resistance. Insulin resistance is a concept derived from blood glucose levels that cannot be decreased even after large doses of insulin are administered [1]. Insulin resistance is affected by adipocytokines secreted from fat tissue,

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systemic cytokines, and many other factors, and it is generally accepted that it is associated with obesity [2]. The number of obese people is increasing globally [3], and considerable attention is being paid to the metabolic syndrome, the main condition of insulin resistance. It has been reported that metabolic syndrome increases the risk of cardiovascular disease by 1.53–2.18-fold, and overall mortality risk increases by 1.27–1.60-fold [4–6]. Thus, the assessment of insulin resistance is important in daily clinical practice.

The three principal methods for assessing insulin resistance are the glucose clamp technique [7], the 1985 published method of homeostatic model assessment (HOMA) [8], and the minimal model method [9]. Since then, numerous other methods and clinical indicators have been proposed. Today, the euglycemic clamp technique is considered the gold standard [10–12] for assessing insulin resistance, and the precision of other techniques should be evaluated against this method. Body composition analyzers using bioelectrical impedance analysis with InBody770 are used in clinical practice and research facilities in over 70 countries, and they are highly portable, non-invasive, and simple to use. In this study, we tested our hypothesis that body composition determines insulin resistance in patients with treatment-naïve type 2 DM.

2. Materials and methods

2.1. Subjects and protocol

Patients with untreated type 2 DM who visited the Diabetes Care Center of Jinnouchi Hospital between June 2014 and December 2015 were enrolled. Those with already treated diabetes, severe uncontrolled diabetes, diabetic ketoacidosis that needed immediate treatment, uncontrolled severe hypertension, and those who could not remain standing to have an elementary body composition tests were excluded. Hyperinsulinemic-euglycemic clamp examinations were performed to calculate insulin sensitivity index (M/I) values as the reference indicator of insulin resistance. The M/I value was compared with elementary body composition and various clinical parameters. All tests were conducted within 1 week. Written informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the Human Ethics Review Committee of Jinnouchi Hospital.

2.2. Hyperinsulinemic-euglycemic clamp examination

Insulin sensitivity was evaluated by a hyperinsulinemic-euglycemic clamp examination using an artificial pancreas (Nikkiso STG-55, Tokyo, Japan), as reported previously [13]. Insulin was given as intravenous loading doses (starting from 4.77 mU/kg/min and were gradually decreased to 1.67 mU/kg/min; under these conditions, the estimated plasma insulin concentration would be about 100 mU/L) over 10 min followed by a continuous infusion at 1.5 mU/kg/min for 120 min. Plasma glucose concentrations were maintained at 5.5 mmol/L by a variable infusion of 10% glucose. Blood insulin concentration at steady state was measured at the time of termination of the hyperinsulinemic-euglycemic clamp examination (I value). Because of variations in the insulin clearance rate for each patient, it has been reported that the actual blood insulin concentrations during hyperinsulinemic -euglycemic clamp test are different from the calculated insulin levels [14]. To correct for the effect of the variability in insulin concentrations among individual patients, we adopted an M/I value as an index of insulin sensitivity, which was a value calculated by dividing the M value by the steady-state serum insulin value (I) in this study. This value indicates the glucose utilization per 1 unit of blood insulin and is a good index representing tissue insulin sensitivity [7].

2.3. Measurement of body fat and muscle composition

Elementary body composition was measured using a direct segmental multi-frequency bioelectrical impedance analyzer (InBody770; Biospace, Seoul, Korea). This analyzer processes 30 impedance measurements by using six different frequencies (1, 5, 50, 250, 500, 1000 kHz) at each of five segments of the body (right arm, left arm, trunk, right leg, left leg) and 15 reactance measurements using tetrapolar 8-point tactile electrodes at three different frequencies (5, 50, 250 kHz) at each of five segments of the body (right arm, left arm, trunk, right leg, left leg) [15,16]. The body composition analysis was conducted within 1 week of the hyperinsulinemic-euglycemic clamp examination.

2.4. Blood sampling and measurement of clinical parameters

Fasting blood samples were collected from the antecubital vein in the morning. Blood analyses were conducted in the hospital laboratory for the measurement of blood glucose, glycated hemoglobin (HbA1c), lipids, creatinine and insulin. The quantitative insulin sensitivity check index (QUICKI) was calculated using the formula: QUICKI = 1/(log(fasting insulin μU/mL) + log(fasting glucose mg/dL)). The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using the formula: HOMA-IR = fasting plasma glucose (mmol/L) × fasting plasma insulin (μIU/ml)/22.5.

2.5. Statistical analysis

The Shapiro–Wilk test was used to assess the normal distribution of continuous data. Data were expressed as mean ± SD, whereas those with skewed distributions were expressed as the median value with interquartile range. Categorical data were presented as frequencies and percentages. Differences between two groups were tested with Fisher's exact test for categorical variables. Differences in continuous variables were analyzed by the unpaired *t*-test or Mann–Whitney U test, as appropriate. Calculation of Spearman's partial correlation coefficient was used to examine the relationships between the independent variables used in the multivariate analysis. As this time, parameters other than the two pairs for calculating the correlation coefficient were used for all control variables. Simple regression analysis was used to eval-