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Diabetes & Metabolism 40 (2014) 161–164

Short report

Measurement of muscle insulin sensitivity in obese men

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Received 8 September 2013; received in revised form 21 October 2013; accepted 29 October 2013

Abstract

Aims. – In 2007, a novel estimate of skeletal muscle insulin sensitivity was derived from the oral glucose tolerance test (OGTT). The aim of this investigation is to assess whether and to what extent the proposed index of skeletal muscle insulin sensitivity derived from the OGTT was associated with muscle insulin sensitivity measured using the hyperinsulinemic-euglycaemic clamp technique.

Methods. – Forty-six middle-aged, abdominally obese men (age 44 ± 8 years, waist circumference 107.4 ± 6.2) were studied. Each participant participated in a 2-hour, 75-g OGTT and a 3-hour hyperinsulinemic-euglycaemic clamp protocol.

Results. – The OGTT-derived index of muscle insulin sensitivity correlated with muscle insulin sensitivity measured with the insulin clamp ($r = 0.55$, $P < 0.01$), however, the standard error of estimate (SEE) when predicting muscle insulin sensitivity by the OGTT-derived index was 5.3 (50%).

Conclusion. – Our findings suggest that despite a statistically significant association between the two methods, the OGTT approach lacks precision and is not a useful method for estimating skeletal muscle insulin sensitivity in abdominally obese men.

Keywords: Skeletal muscle insulin resistance; Glucose tolerance; Abdominal obesity

1. Introduction

Skeletal muscle insulin resistance is both an antecedent [1] and a characteristic of type 2 diabetes [2], and thus the need to obtain accurate estimates of skeletal muscle insulin resistance feasibly in clinical practice is paramount. Attempts have been made to estimate insulin sensitivity from measurements of glucose and insulin during the oral glucose tolerance test (OGTT) [3–5]. While these estimates correlate reasonably well with muscle insulin sensitivity measured using the hyperinsulinemic-euglycaemic clamp technique, they are not specifically designed to assess the distinct contributions of the liver or skeletal muscle towards whole-body insulin sensitivity. In 2007, Abdul-Ghani et al. proposed a novel estimate of skeletal muscle insulin sensitivity derived from the 75 g OGTT which aims to eliminate the contribution of the liver towards whole-body insulin sensitivity [6]. Here, skeletal muscle insulin sensitivity was calculated as the rate of decline in plasma glucose concentration from its peak value to its nadir divided by the mean plasma insulin concentration. It was demonstrated that the OGTT-derived index of skeletal muscle insulin sensitivity correlated strongly with skeletal muscle insulin sensitivity measured with the insulin clamp ($r = 0.78$, $P < 0.0001$). Although Abdul-Ghani et al. demonstrated a strong association between the two indices of muscle insulin sensitivity, the error in predicting muscle insulin sensitivity was not reported.

To our knowledge, the association between the OGTT-derived index of skeletal muscle insulin sensitivity derived by Abdul-Ghani et al. and clamp-measured insulin sensitivity has not been confirmed. Therefore, in this study we attempt to replicate the observations made by Abdul-Ghani et al. by measuring skeletal muscle insulin sensitivity in a sample of men with the high-risk form of obesity [7] using both the hyperinsulinemic-euglycaemic clamp and OGTT methods. The primary aim of this investigation was to assess: (1) the strength of the association between the OGTT-derived index of skeletal muscle insulin sensitivity created by Abdul-Ghani et al. and insulin sensitivity measured using the criterion clamp technique and (2) the standard error of estimate when predicting muscle insulin sensitivity using the OGTT-derived muscle insulin sensitivity index.

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1262-3636/$ – see front matter
http://dx.doi.org/10.1016/j.diabet.2013.10.005

2. Methods

2.1. Participants

Forty-six abdominally obese, middle-aged men initially recruited for participation in an exercise trial. All participants were sedentary, non-smokers, and Caucasian.

2.2. Measurement of skeletal muscle insulin sensitivity by hyperinsulinemic-euglycaemic clamp

Participants consumed a weight-maintenance diet consisting of at least 200 g of carbohydrate for a minimum of 4 days and were asked to avoid strenuous physical activity for 3 days before insulin sensitivity was measured. All studies were performed at about 8:00 a.m. after a 12- to 14-hour overnight fast. An antecubital vein was catheterized for infusion of insulin and 20% glucose. An intravenous catheter was inserted in a retrograde fashion in a hand vein, and the hand was placed in a heating pad for sampling of arterialized blood. Insulin was infused at a rate of 40 mU/m^2 per minute for 3 hours. Plasma glucose was measured using an automated glucose analyzer (YSI 2300 Glucose Analyzer, YSI, Yellow Springs, Ohio) every 5 minutes in arterialized blood.

Insulin sensitivity was measured as the glucose disposal rate (M) divided by steady state plasma insulin (SSPI). The glucose disposal rate was calculated as the average exogenous glucose infusion rate during the final 30 minutes of euglycaemia and expressed per kilogram of skeletal muscle mass as measured by magnetic resonance imaging. SSPI was calculated as the average plasma insulin concentration during the final 30 minutes of euglycaemia.

Participants with an M less than 8.3 mg/min/kg skeletal muscle mass were classified as insulin resistant as this was the mean M per kilogram skeletal muscle mass previously observed in T2D subjects in our research unit [8].

2.3. Measurement of skeletal muscle insulin sensitivity by OGTT

A 2-hour, 75-g oral glucose tolerance test was administered the morning after an overnight fast. The OGTT was performed within 3 days of the clamp test. Blood samples were collected from the antecubital vein at −15, 0, 30, 60, 90, and 120 minutes. Glucose was measured by using an automated glucose analyzer (YSI), and insulin was measured by using a radioimmunoassay kit (Intermedico, Toronto, Ontario, Canada).

The rise in plasma glucose concentration during the OGTT stimulates increased disposal of glucose from the blood, primarily into skeletal muscle. Since the rate of hepatic glucose production (HGP) does not change significantly during the final 60 minutes of the 2 hour OGTT [9], the decline in the plasma glucose concentration in the final 60 minutes of the OGTT should primarily reflect glucose uptake into skeletal muscle [6]. Given that the decline from the peak plasma glucose concentration during the OGTT is determined by the combination of muscle insulin sensitivity and the concentration of insulin in the plasma, skeletal muscle insulin sensitivity was calculated as the rate of decline in plasma glucose concentration (dG/dt) divided by mean plasma insulin concentration (MPI). Specifically, dG/dt was calculated as the slope of the line of least square fit for the decline in plasma glucose concentration from its peak to its subsequent nadir during the OGTT. MPI was calculated as the average plasma insulin concentration during the 2-hour OGTT obtained from measurements at 30, 60, 90, and 120 minutes.

The Matsuda index [3], Stumvoll formula [4], and Mari's OGIS [5] were calculated to determine their associations with clamp-measured insulin sensitivity.

3. Results

Participants were abdominally obese (waist circumference [WC] 107.4 ± 6.2 cm, BMI 31.5 ± 2.0 kg/m^2) and middle-aged (44 ± 8 years). Of the 46 men, 8 were classified as insulin resistant and 36 were insulin sensitive.

A significant correlation was observed between muscle insulin sensitivity measured with the hyperinsulinemic-euglycaemic clamp and muscle insulin sensitivity derived from the OGTT ($r = 0.55$, $P < 0.01$, Fig. 1). The standard error of estimate when predicting muscle insulin sensitivity from the OGTT-derived index was 5.3 (50%). Further analysis revealed that the association was significant in insulin sensitive subjects ($r = 0.51$, $P < 0.01$, SEE = 47%) but not in those with insulin resistance ($P > 0.9$).

We also determined the associations between euglycaemic clamp measures of skeletal muscle insulin sensitivity with corresponding estimates obtained using commonly employed methods. Indeed, significant associations were observed between the glucose disposal rate and OGTT-derived measures

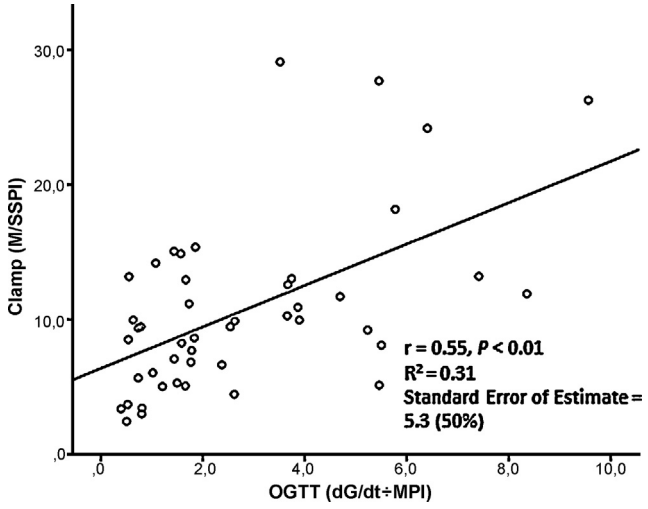

Fig. 1. Relation between muscle insulin sensitivity as measured directly by the hyperinsulinemic-euglycaemic clamp (M/SSPI) and the OGTT-derived index of muscle insulin sensitivity (dG/dt÷MPI). M = glucose disposal rate; SSPI = steady state plasma insulin concentration; dG/dt = rate of decline in plasma glucose concentration from peak to nadir; MPI = mean plasma insulin concentration during the OGTT.