Endocrine Journal 2014, **61** (1), 77-83

ORIGINAL

Lean mass inversely predicts plasma glucose levels after oral glucose load independent of insulin secretion or insulin sensitivity in glucose intolerance subjects

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Abstract. Muscle mass inversely relates to 2 hours glucose levels after oral glucose load in non-diabetic subjects. A study in glucose intolerance subjects has never been performed. We conducted this study to determine the relationship between muscle mass and glucose level after oral glucose load in glucose intolerance subjects. Sixty Thai subjects, 44 drug-naïve, newly diagnosed type 2 diabetes mellitus and 16 impaired glucose tolerance were studied. The 180 min 75 g oral glucose tolerance test was performed. Total body fat and lean mass were measured by dual-energy x-ray absorptiometry. Insulin sensitivity was determined by insulin sensitivity index using model of Matsuda & DeFronzo. The 1st-phase and total insulin secretion were determined from glucose tolerance data. Pearson correlation and linear regression were used for the analysis. Lean mass was inversely correlated with area-under-curves of glucose 0-180 min (r =-0.320; p=0.013). The relationship was significant after adjustment with age and body-mass-index (r =-0.350; p=0.007). Area-under-curves of glucose 0-180 min was correlated with height (r =-0.282; p=0.029), fasting glucose (r =0.742; p<0.0001), log area-under-curves of insulin 0-180 min (r =-0.258; p=0.047) and log 1st-phase insulin secretion (r =-0.518; p<0.0001). By multivariate analysis, fasting glucose (standardized β=4.54; p<0.001), log 1st-phase insulin secretion (standardized β=-43.09; p=0.005) and lean mass (standardized β=-0.003; p=0.011) were the significant parameters predicting area-under-curves of glucose 0-180 min. In conclusion, lean mass inversely predicted glucose levels after oral glucose load independent of insulin secretion and insulin sensitivity in glucose intolerance subjects.

Key words: Impaired glucose tolerance, Lean mass, Oral glucose tolerance test, Postprandial hyperglycemia, Type 2 diabetes mellitus

THE EPIDEMIOLOGIC STUDIES in several populations indicate that 2 hours plasma glucose levels after an oral glucose tolerance test (OGTT) and prevalence of impaired glucose tolerance were higher in non-diabetic women than non-diabetic men [1-3]. Our previous study in lean, non-diabetic Thai subjects also supported those findings [4]. The mechanism by which the 2 hours plasma glucose levels after OGTT are higher in women is unclear. Lower height and/or lesser fat-free mass of women have been shown to be the factors [5-7]. Our study showed that it was the lower skeletal muscle mass of women, not sex or lower height, that predicted higher 2 hours plasma glucose levels after oral glucose load (post-load plasma glucose) independent of insulin secretion and insulin sensitivity [4]. Since skeletal muscle is a major organ of insulin-dependent glucose uptake and glucose utilization particularly at postprandial state, such association is theoretically sound. However, there are some studies that contradict our results. Brochu *et al*. [8] and Comerford *et al*. [9] reported a positive association whereas Kuk *et al*. [10] found no association of lean mass and post-load plasma glucose levels in obese, non-diabetic subjects. The inconsistent findings of the association between

Submitted Jun. 10, 2013; Accepted Oct. 3, 2013 as EJ13-0241
Released online in J-STAGE as advance publication Oct. 22, 2013
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lean mass and post-load plasma glucose levels could be the degree of muscle insulin resistance of obese subjects in those studies which overcomes the mass effect of muscle glucose uptake. There is a knowledge gap between the association of the severity of glucose intolerance and the effect of lean mass on post-load glucose level. Previous studies included patients with very severe insulin resistance and normal glucose tolerance subjects. To our knowledge, a study of the association of lean mass and post-load glucose level in pre-diabetic and mild diabetic subjects has never been performed. The objective of this study was to test the hypothesis that muscle mass was inversely associated with and predicted the variation of post-load plasma glucose levels in glucose intolerance subjects.

Materials and methods

Patient recruitment was done by three methods. Firstly, apparently healthy volunteers who previously participated in an OGTT study who fit our inclusion criteria were consecutively invited to participate in this study. Secondly, high risk patients with impaired fasting glucose, hypertension, or dyslipidemia who were followed up at an out-patient clinic were invited and the third method was to invite drug-naïve diabetic patients who attended at out-patient clinic. Exclusion criteria were patients taking any anti-diabetic drugs, taking any medication affecting glucose metabolism (*i.e*. systemic glucocorticoid, high-dose diuretic, or estrogen, recent illness within 2 weeks prior to the study, pregnancy, regular strenuous exercise and regular consumption of alcohol greater than 2 drinks per day. Sixty Thai subjects in this study included 31 women and 29 men. Of the 60 subjects 44 were newly diagnosed drug-naïve patients with type 2 diabetes mellitus and 16 patients were impaired glucose tolerance (IGT) subjects. Type 2 diabetes mellitus was defined by the positive of at least two of the following criteria, fasting plasma glucose (FPG) $\geq$ 126 mg/dL or 2 hours plasma glucose after 75 g OGTT $\geq$ 200 mg/dL or HbA1c (standardized by National Glycohemoglobin Standardization Program) $\geq$ 6.5%. Impaired glucose tolerance was defined by FPG <126 mg/dL and 2 hours plasma glucose 140-199 mg/dL after 75 g OGTT. Dual-energy x-ray absorptiometry was performed on the day of OGTT. Physical activity levels were assessed using the Thai version of the Short Format International Physical Activity Questionnaire [11, 12]. All were advised not to have strenuous exercise and to stop smoking and alcohol drinking for at least 24 hours before the study.

The study was performed at Ramathibodi Hospital, Bangkok and at Songklanagarind Hospital, Songkhla using the same protocol. Subjects gave written informed consent before the beginning of the study. The study protocol was approved by Ramathibodi Hospital and Songklanagarind Hospital Ethical Committees.

2.1 OGTT and dual-energy x-ray absorptiometry

The 180 min 75 g OGTT was performed in the morning after an overnight fast. Blood was collected *via* retained intravenous catheter before and at 30, 60, 120 and 180 min after glucose ingestion for measurement of glucose and insulin. Total body fat and total lean mass were measured by dual-energy x-ray absorptiometry standard software. The DEXA with enCORE 2003 software version 7.53 and the DEXA with Prodigy software version 4.7 were used at Ramathibodi Hospital. The DPX-MD (Lunar Corp., Madison, WI, USA) was used at Songklanagarind Hospital. All DEXA devices are from the same manufacturer and have similar high precision for the measurement of body composition [13]. Total lean mass measured by DEXA has been shown to be highly correlated with total skeletal muscle mass (R = 0.94) by multi-slice magnetic resonance imaging in healthy adults [14].

2.2 Insulin sensitivity and insulin secretion measurements

Whole body insulin sensitivity was measured by insulin sensitivity index (ISI) using the OGTT model of Matsuda & DeFronzo [15] (ISI = 10,000/square root of [(fasting glucose X fasting insulin) X (mean glucose X mean insulin during OGTT)]). Data from type 2 diabetic Thai subjects suggested that ISI by the model of Matsuda & DeFronzo had good correlation with muscle insulin sensitivity by euglycemic hyperinsulinemic clamp (r =0.679) (Rattarasarn C, unpublished data).

The 1st-phase insulin secretion was calculated from the ratio of the incremental insulin and glucose concentrations at 30 minutes above basal after OGTT. Data from normal and diabetic subjects indicated that 1st-phase insulin secretion from OGTT model had a good correlation with the standard method of intravenous glucose tolerance test [16, 17]. Total insulin secretion was calculated as the area under the curves (AUC) of plasma insulin (0-180 min) after oral glucose load (AUCins0-180 min).

2.3 Biochemical analysis

Blood for plasma insulin was collected and frozen at -80°C until analysis, all within 1 month after collection. Plasma insulin was measured by immunochemiluminescence (Immulite 2000, Diagnostic Products Corp, Los Angeles, CA). Glucose was measured by the hexokinase method (Dimention RxL, Dade Behring Co. Ltd, New York, USA). HbA1c was measured by the Turbidimetry technique (Cobas Integra 400 plus, Roche).

2.4 Statistical analysis

Data were expressed as mean ± SD or median and quartile depending on the type of data distribution. Correlation coefficients were determined by Pearson product moment. Multiple linear regression analysis was performed to identify independent factors contributing to variances of AUC of post-load plasma glucose levels. All factors with p values ≤ 0.2 from univariate analysis were entered into the regression model. Factors previously known to be associated with post-load plasma glucose levels but had p values > 0.2 were also forced into the regression model. Any variable that was not normally distributed was log-transformed prior to analysis. All statistical analyses were performed using SPSS version 17.0 for Windows (SPSS, Chicago, IL) and R program. AUC was calculated by the trapezoidal rule. P<0.05 was considered statistically significant.

Results

Clinical characteristics of subjects and parameters of insulin secretion and insulin sensitivity are shown in Table 1. Seven of 31 (22.6%) women and 9 of 29 (31.0%) men had impaired glucose tolerance. HbA1c of type 2 diabetic subjects at the time of study was 6.7 ± 0.6%. Of the subjects whose physical activity levels were assessed, 62.5% and 34.4% were categorized as having low (less than 600 MET-minutes/week) and moderate (600-2,999 MET-minutes/week) physical activity, respectively. By univariate analysis, AUC of plasma glucose for 0-180 min after OGTT (AUCglu0-180 min) was correlated with height (r = -0.282, p = 0.029), FPG (r = 0.742, p < 0.0001), log AUCins0-180 min (r = -0.258, p = 0.047), lean mass (r = -0.320, p =

Table 1 Clinical characteristics of subjects (N=60)

	Total (N=60)	Diabetes (N=44)	IGT (N=16)
Age (y)	55.4 ± 12.2	58.4 ± 12.0	46.3 ± 8.0
Weight (kg)	68 ± 11.1	67.2 ± 10.4	70.2 ± 12.7
Height (m)	1.59 ± 7.96	1.58 ± 7.34	1.61 ± 9.33
BMI (kg/m^2)	26.8 ± 3.9	26.8 ± 4.2	26.7 ± 3.0
Waist circumference (cm)	91.0 ± 10.0	90.9 ± 9.6	91.0 ± 11.0
Total body fat (kg)	23.3 ± 7.6	23.8 ± 8.5	21.8 ± 4.1
Total lean mass (kg)	42.1 ± 8.7	40.8 ± 7.4	45.3 ± 11.2
Physical activity levels (MET-min/wk)[a]		420 (305 – 724)	-
Glucose levels (mg/dL) after 75-g OGTT			
0 min	108.6 ± 16.2	113.4 ± 15.0	95.3 ± 11.0
30 min	194.3 ± 32.1	200.1 ± 31.1	178.0 ± 29.8
60 min	236.3 ± 45.6	248.4 ± 42.9	203.0 ± 35.6
120 min	218.6 ± 53.4	238.8 ± 47.2	163.0 ± 18.8
180 min	144.0 ± 58.8	157.0 ± 62.9	108.2 ± 19.5
Insulin level (μU/mL) after 75-g OGTT[b]			
0 min	7.4 (3.4 – 12.8)	5.0 (2.3-12.3)	9.8 (6.7-14.6)
30 min	29.2 (18.2 – 54.8)	23.4 (14.4-41.1)	43.3 (31.7-104.2)
60 min	45.6 (30.0 – 84.8)	40.1 (26.2-65.7)	74.4 (43.9-123.0)
120 min	71.0 (40.0 – 109.1)	71.0 (34.0-104.2)	81.9 (47.4-117.2)
180 min	36.1 (16.3 – 77.6)	35.7 (14.4-83.8)	39.5 (21.8-71.7)
ISI[b]	3.9 (2.7 – 7.0)	5.1 (2.7-10.5)	3.4 (2.5-4.6)
1st– phase insulin secretion[b]	0.27 (0.15 – 0.46)	0.19 (0.14-0.41)	0.38 (0.32-1.01)
Total insulin secretion (μU/mL·h)[b]	160.1 (95.9 – 246.8)	141.2 (81.3-222.5)	176.1 (124.8-313.2)

Data are expressed as mean ± SD or median and quartile. [a] Data was obtained from 37 subjects. [b] Log-transformed prior analysis. To convert glucose to mmol/L, multiply by 0.056. To convert insulin to pmol/L, multiply by 6.0. ISI, insulin sensitivity index; IGT, impaired glucose tolerance subjects; 1st-phase insulin secretion, increment of insulin/glucose 0-30 min of OGTT; Total insulin secretion, area under the curves (AUC) of insulin 0-180 min.

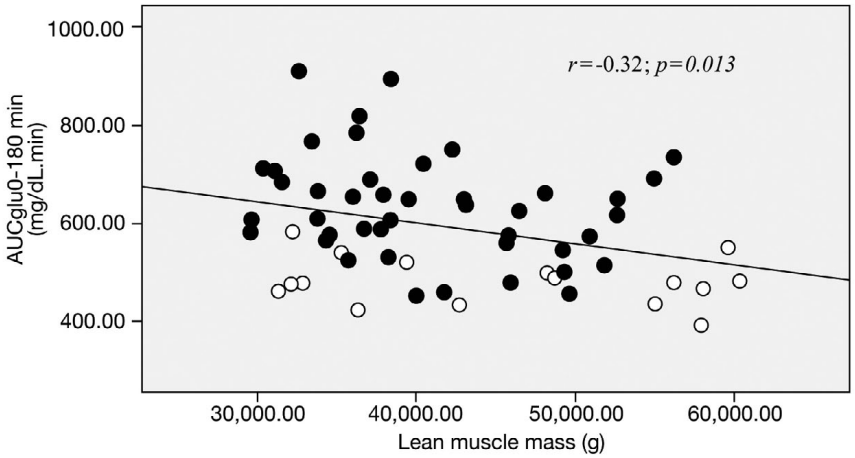

Fig. 1 Correlation of lean mass and area under the curves of plasma glucose after oral glucose load in IGT (○) and type 2 diabetic (●) subjects. To convert glucose to mmol/L, multiply by 0.056

Table 2 Predictors of area under the curves of plasma glucose 0-180 min after oral glucose load by multivariate linear regression analysis

Predictors	Adjusted R^2	Standardized coefficient (β)	Standard error	*P*
	0.663[a]			
Fasting plasma glucose		4.54	0.62	<0.001
Log 1st-phase insulin secretion		-43.09	14.66	0.005
Lean mass		-0.003	0.001	0.011
Log $AUC_{ins0\text{-}180\ min}$		38.77	20.75	0.067
Height		-0.25	2.6	0.92
Total fat mass		0.00009	0.001	0.95
Log ISI		-1.94	33.22	0.95

[a] FPG, log 1st-phase insulin secretion, lean mass and Log $AUC_{ins0\text{-}180\ min}$

0.013) and log 1st-phase insulin secretion (r = -0.518, $p < 0.0001$). Fig. 1 showed the inverse correlation of lean mass and AUCglu0-180 min. The correlation of lean mass and AUCglu0-180 min was still significant (r = -0.350, $p = 0.007$) after adjustment with age and BMI. Log ISI was not correlated with AUCglu0-180 min in univariate analysis but was entered into the regression model since it was shown to predict post-load plasma glucose levels by several studies.

The height, FPG, log 1st-phase insulin secretion, log AUCins0-180 min, lean mass, total fat mass and Log ISI were included in the multivariate linear regression analysis. Only FPG, log 1st-phase insulin secretion and lean mass were the significant parameters predicting AUCglu0-180 min (Table 2). The model explained 66.3% of the variance of AUCglu0-180 min.

Discussion

This study demonstrated that lean mass was inversely associated with and independently predicted post-load plasma glucose levels in glucose intolerance subjects. Since lean mass has been shown to be strongly correlated with skeletal muscle mass [14], it can be assumed that it is the skeletal muscle mass that influences post-load plasma glucose levels in this study. It indicates that in addition to insufficient insulin secretion and insulin resistance, having low skeletal muscle mass per se can result in hyperglycemia after oral glucose load in glucose intolerance subjects. This finding confirms the role of muscle in glucose metabolism similar to our previous study in normal glucose tolerance subjects.

Skeletal muscle is known to be an important site of glucose uptake particularly in the postprandial state.

The presence of muscle insulin resistance together with the insufficient insulin secretion can cause postprandial hyperglycemia in glucose intolerance subjects. The interesting finding in this study was the role of muscle in lowering post-load glucose independent of insulin secretion and insulin sensitivity. This insulin-independent glucose up-take or glucose effectiveness has been studied intensively [18-20]. In non-obese subjects who are under a euglycemic condition, the skeletal muscle contributes 13% to glucose effectiveness but with a hyperglycemic condition in the same subjects, muscle could up-take glucose up to 38% of the whole body even when insulin secretion was abolished [21]. Similar findings of being lean had higher glucose effectiveness were reported by Gastaldelli *et al*. but with a larger population [18]. Our study provided additive information of lean mass and glucose effectiveness that even with a physiologic insulin level, muscle mass is the predictor of post-load glucose effectiveness in people with impaired glucose tolerance and early diabetes. From the SAM study [18], the results were from a euglycemic hyperinsulinemic clamp, which may be different from the physiology of an OGTT which was also demonstrated in a paper by Henriksen *et al*. [22]. Marcus *et al*. reported that after 16 weeks of light resistance exercise in elderly type 2 diabetic subjects, an increase of lean mass and regional muscle glucose uptake was observed with no significant change of whole body muscle insulin sensitivity [23]. This indicates that the increase of muscle mass by itself can increase its capacity to uptake glucose.

Venn *et al*. [24] and Dickinson *et al*. [25] reported that lean, healthy young adult Asians had higher plasma glucose levels after oral glucose or mixed meal ingestion than age- and BMI-matched Caucasians. Lower insulin sensitivity was associated with higher postprandial plasma glucose levels only in the latter but not the former studies. Likewise, Asian type 2 diabetic subjects appear to have higher postprandial plasma glucose levels than those of Caucasians despite similar HbA1c levels [26, 27]. Whether the ethnic difference of muscle mass between Asians and Caucasians may explain the difference of postprandial plasma glucose levels of those studies is not known. Our group previously reported a negative association of muscle mass and post-load plasma glucose levels in insulin-sensitive lean subjects [4]. This study supports and extends our findings to insulin-resistant, glucose intolerant obese subjects. Although physical activity is known to affect muscle mass and post-load plasma glucose levels, it is unlikely to be a factor in this study since most of our subjects have low to moderate physical activity levels. Furthermore, no correlation of physical activity levels and lean mass or AUCglu0-180 min was observed in this study (data not shown).

However, there were some different findings of muscle mass and glucose metabolism. Brochu *et al*. [8] and Comerford *et al*. [9] respectively studied the relationships of post-load plasma glucose levels, lean mass index (lean mass divided by height square) and insulin sensitivity in postmenopausal women and women with polycystic ovary syndrome. They independently found a positive association of lean mass index and plasma glucose levels and a negative association of lean mass index and insulin sensitivity. These findings are in contrast with our study. The discrepancy is unlikely to be from a different method of lean mass measurement since even though we used lean mass index in place of the absolute amount of lean mass, the results were not different (data not shown). The differences of subject characteristics between their studies and ours may explain these contradictory results. Despite the similar lean mass index, subjects of the Brochu *et al*. and Comerford *et al*. studies were more obese (BMI > 30 kg/m^2) and had higher insulin resistance than ours. It is conceivable that severe insulin resistance from marked obesity may overcome the mass effect of muscle on glucose uptake capacity in those studies.

This study has several limitations. Firstly, the causal relationship of lean mass and post-load plasma glucose levels cannot be proven with the cross-sectional design of this study. A prospective follow-up or interventional study is required to verify this concept. Secondly, it might have been the muscle fiber type composition and not the muscle mass itself that determines post-load plasma glucose levels [28]. However, since most of the subjects in the study have sedentary lifestyles, it is less likely that those who have larger muscle mass would have greater high oxidative muscle fiber type. Thirdly, it is uncertain whether the inverse relationship of lean mass and plasma glucose levels could be demonstrated with mixed meal challenge. Although plasma glucose excursion after oral glucose load and after mixed meal have been shown to be closely correlated in non-diabetic and diabetic subjects, the peak levels of plasma glucose and plasma insulin are lower by the latter test [29, 30]. Fourthly, the findings of this study may not be applied to advanced type 2 diabetic subjects who have

more severe impairment of insulin secretion or insulin sensitivity since insulin secretion and insulin sensitivity are the stronger determinants of postprandial plasma glucose levels. Lastly, our insulin secretion and sensitivity index were obtained by using the same OGTT data. Ideally, these data would be evaluated by independent measures to avoid auto-correlation.

In conclusion, this study demonstrated the inverse relationship of lean mass and post-load plasma glucose levels in subjects with glucose intolerance. The effect of lean mass on post-load plasma glucose levels was independent of insulin secretion or insulin sensitivity. The causal relationship of lean mass and post-load or postprandial plasma glucose levels needs to be confirmed. The clinical significance of lean mass to glycemic control in patients with type 2 diabetes is uncertain and needs further exploration.

Acknowledgements

This study was supported by research funds from Faculty of Medicine, Ramathibodi Hospital and The Endocrine Society of Thailand.

Conflict of Interest

The authors have no conflicts of interest to declare.

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