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SHORT REPORT

Shape of the glucose response curve during an oral glucose tolerance test is associated with insulin clearance and muscle insulin sensitivity in healthy non-obese men

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Keywords
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ABSTRACT

Individuals with a monophasic glucose response curve (GRC) during a 75-g oral glucose tolerance test have a higher risk for type 2 diabetes than those with a biphasic GRC. However, no studies have addressed the association between GRC type and insulin clearance. Thus, we studied 49 healthy non-obese Japanese men. We divided study participants into the monophasic or biphasic group based on the shape of their GRC. We evaluated tissue-specific insulin sensitivity and insulin clearance using a two-step hyperinsulinemic-euglycemic clamp. The monophasic group had more visceral fat, lower insulin clearance and lower muscle insulin sensitivity than the biphasic group, whereas liver and adipose tissue insulin sensitivity, and insulin secretion were comparable. In conclusion, healthy non-obese men with a monophasic GRC have lower insulin clearance and muscle insulin sensitivity.

INTRODUCTION

To prevent type 2 diabetes, an optimal screening method for identifying individuals at high risk should be developed. Glucose levels during a 75-g oral glucose tolerance test (OGTT) are used to diagnose diabetes. Recently, independent of glucose levels, the shape of the glucose response curve (GRC) during an OGTT has been recognized as a risk factor for type 2 diabetes development[1,2]. When the shape of the GRC is classified as monophasic or biphasic based on glucose concentrations during OGTT, individuals with a monophasic curve have a higher risk for type 2 diabetes than those with a biphasic curve[1,2].

However, the pathophysiological features of each type are not fully understood. Some reports have suggested that a monophasic curve is associated with impaired insulin secretion and decreased insulin sensitivity compared with a biphasic curve[3,4]. However, the metabolic features of both types of curves in apparently healthy non-obese individuals have not been elucidated yet.

Some data support the hypothesis that decreased insulin clearance is primarily observed in healthy individuals and might elicit insulin resistance, suggesting that reduced insulin clearance could be a upstream risk factor for the onset of type 2 diabetes[5]. Our group showed impaired insulin clearance even in apparently healthy non-obese men, and this is associated with modestly lower insulin sensitivity in muscle[6]. However, no studies have addressed the association between GRC type and insulin clearance.

Thus, the present study investigated the association between the shape of the GRC during an OGTT and tissue-specific insulin sensitivity, insulin clearance and insulin secretion in healthy, non-obese Japanese men.

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METHODS

Study participants

The shape of the GRC was evaluated in participants of the Sportology Center Core Study[7]. To assess the role of the shape of the GRC in apparently healthy non-obese men, we chose those with a body mass index of 21.0 to <25.0 kg/m^2 and no risk factors for cardiovascular disease. We defined cardiometabolic risk factors assessed in the present study as hyperglycemia, dyslipidemia and hypertension[7]. The ethics committee of Juntendo University approved this study, and this study was carried out in accordance with the principles outlined in the Declaration of Helsinki.

Study design

We carried out the OGTT and a two-step hyperinsulinemic-euglycemic clamp with a glucose tracer. Each step lasted 180 min, with a constant insulin infusion rate of 10 mU/m^2/min at the first step, and 20 mU/m^2/min at the second step. Intrahepatic lipid and intramyocellular lipid levels were measured with ^{1}H-magnetic resonance spectroscopy[8]. The percentage of body fat and fat-free mass were measured using the bioimpedance method (InBody 720; Biospace, Tokyo, Japan). Furthermore, the abdominal visceral fat area and subcutaneous fat area were also estimated by magnetic resonance imaging. These methods have been previously reported in detail[7].

Calculations

GRC type was defined based on glucose concentrations during the 2-h OGTT. A monophasic GRC was defined as a gradual increase in glucose concentration until a peak was reached and followed by a subsequent >4.5 mg/dL decrease in glucose concentration. A biphasic GRC was defined as having a >4.5 mg/dL rise in glucose concentrations after the decline in glucose concentrations[3,4].

Muscle, liver and adipose tissue insulin sensitivity and metabolic clearance rate of insulin (MCRI) were evaluated using a two-step hyperinsulinemic-euglycemic clamp[6,7,9].

Statistical analysis

Data are shown as the mean ± standard deviation. Data that did not have a normal distribution were log-transformed as required. We compared the data using an unpaired Student's *t*-test or χ^2-test. All statistical tests were two-sided with a significance level of 5%. We used SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA) for the statistical analyses.

Table 1 | Clinical characteristics of the biphasic and monophasic groups

	Overall (n = 49)	Biphasic group (n = 18)	Monophasic group (n = 31)	P
Age (years)	40.2 ± 5.3	39.9 ± 5.5	40.3 ± 5.2	0.811
BMI (kg/m^2)	23.1 ± 1.0	22.9 ± 1.2	23.2 ± 0.9	0.331
Family history of type 2 diabetes (%)	14 (28.6%)	4 (22.2%)	10 (32.3%)	0.453
Body fat (%)	20.1 ± 5.0	18.8 ± 4.0	20.9 ± 5.4	0.159
Fasting plasma glucose (mg/dL)	93.2 ± 6.8	93.6 ± 6.5	93.0 ± 7.1	0.778
Fasting serum insulin (μU/mL)	4.9 ± 2.1	4.36 ± 1.83	5.20 ± 2.14	0.169
AUC-glucose during OGTT (mg·min/dL·10^3)	15.6 ± 2.3	14.5 ± 1.7	16.2 ± 2.4	**0.008**
AUC-insulin during OGTT (μU·min/mL·10^3)	5.2 ± 2.8	4.4 ± 2.4	5.7 ± 3.0	0.144
Insulinogenic index	0.95 ± 0.68	1.10 ± 0.68	0.86 ± 0.68	0.236
Free fatty acid (μEq/L)	335 ± 105	322.4 ± 110.5	342.6 ± 103.4	0.523
HbA1c (%)	4.9 ± 0.2	4.9 ± 0.2	4.9 ± 0.2	0.701
High-molecular-weight adiponectin (ng/mL)	1.82 ± 1.21	2.01 ± 1.34	1.71 ± 1.14	0.402
Intramyocellular lipid in TA (S-fat/Cre)	3.2 ± 1.9	2.7 ± 1.8	3.5 ± 1.9	0.158
Intramyocellular lipid in SOL (S-fat/Cre)	12.8 ± 6.8	11.7 ± 6.7	13.5 ± 6.9	0.370
Intrahepatic lipid (%)	1.9 ± 3.2	1.8 ± 3.3	2.0 ± 3.3	0.878
Abdominal visceral fat area (cm^2)	75.3 ± 28.0	62.6 ± 24.2	82.7 ± 27.8	**0.014**
Abdominal subcutaneous fat area (cm^2)	106 ± 40	94.2 ± 38.0	113.6 ± 39.9	0.102
VO_{2peak} (mL/kg per min)	36.0 ± 7.0	37.3 ± 8.3	35.2 ± 6.1	0.320
MCRI during the second step	610.9 ± 83.3	641.7 ± 71.9	593.0 ± 85.4	**0.048**
SS_{SI} during the second step (μU/mL)	36.4 ± 5.2	33.8 ± 4.2	37.9 ± 5.2	**0.006**
%Reduction in EGP/SS_{SI} during the first step (%/μU·mL^{-1})	3.7 ± 1.0	3.9 ± 0.9	3.7 ± 0.9	0.424
Rd during the second step (mg/kg FFM·min^{-1})	8.6 ± 2.0	9.1 ± 2.3	8.3 ± 1.8	0.189
Rd/SS_{SI} during the second step (mg/kg FFM·min^{-1} ·μU^{-1}·mL)	0.24 ± 0.08	0.27 ± 0.09	0.22 ± 0.06	**0.020**
%FFA suppression/insulin during the first step (%/μU·mL^{-1})	4.54 ± 1.35	4.57 ± 1.26	4.52 ± 1.42	0.904

Data are the mean ± standard deviation. AUC, area under the curve; BMI, body mass index; Cre, creatine signal; EGP, endogenous glucose production; FFM, fat-free mass; HbA1c, glycated hemoglobin; MCRI, metabolic clearance rate of insulin; OGTT, oral glucose tolerance test; Rd, rate of disappearance; S-fat, methylene signal intensity; SOL, soleus muscle; SS_{SI}, steady-state serum insulin; TA, tibialis anterior muscle. Bold values indicate P values with significant differences between the two groups.

RESULTS

Based on the GRC during the 75-g OGTT, we divided all participants into either the monophasic (n = 31) or biphasic group (n = 18). Glucose and insulin levels were higher in the monophasic group (Table 1; Figure 1). The monophasic group had a significantly higher area under the curve of glucose during the 75-g OGTT than the biphasic group, whereas the area under the curve of insulin and the insulinogenic index were not significantly different between the groups. Although percentage body fat, subcutaneous fat area, intrahepatic lipid and intramyocellular lipid were comparable between the two groups, the monophasic group had significantly higher visceral fat area. MCRI was lower in the monophasic group, which contributed to increased insulin levels during the clamp. Muscle insulin sensitivity was significantly lower in the monophasic group. The rate of disappearance, mainly reflecting muscle glucose uptake, was comparable between the groups. These data suggest that the rate of disappearance was maintained by increased steady-state serum insulin due to lower insulin clearance in the monophasic group. Adipose tissue and hepatic insulin sensitivity were comparable between both groups.

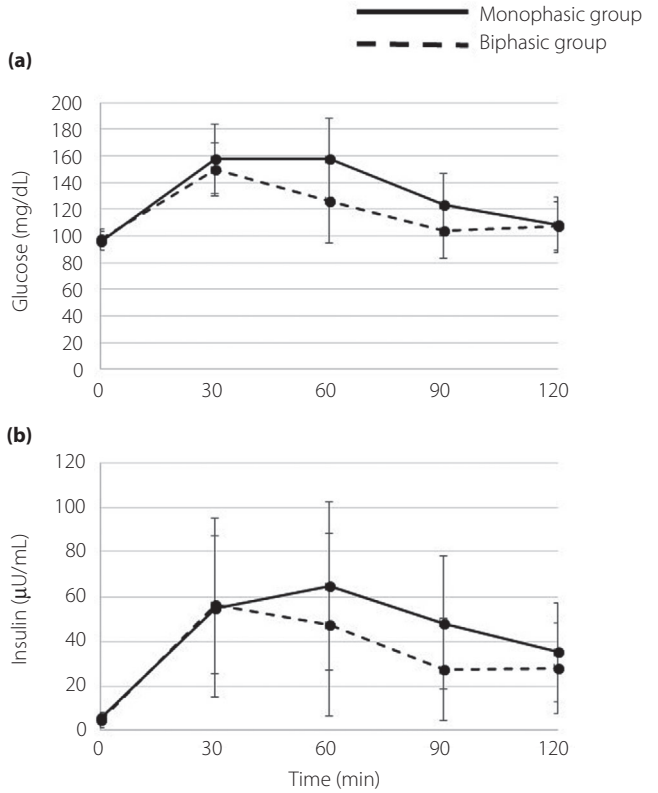

Figure 1 | (a) Plasma glucose and (b) insulin levels during oral glucose tolerance tests in individuals in the monophasic group (solid lines) and biphasic group (dashed lines). Data are reported as the mean ± standard deviation.

DISCUSSION

Recent data suggest that decreased insulin clearance might elicit insulin resistance and thus increase the risk of type 2 diabetes[5,6,10,11]. Individuals with a monophasic curve are at higher risk for future type 2 diabetes[1,2], but the association between GRC type and insulin clearance has not been addressed. The present study showed that healthy non-obese men with a monophasic GRC during OGTT have more visceral fat, lower insulin clearance and lower muscle insulin sensitivity.

We showed that decreased insulin clearance is observed even in apparently healthy men, which seems to be a compensatory mechanism for maintaining glucose uptake with modest muscle insulin resistance[6]. Similarly, in the present study, modest insulin resistance in participants with a monophasic curve was compensated by decreased MCRI. Thus, low MCRI could be viewed as early metabolic change compensating for modest insulin resistance. In contrast, several animal models showed that impaired insulin clearance and resulting hyperinsulinemia are not compensatory mechanisms against insulin resistance, but rather could be upstream factors that induce the development of insulin resistance and adiposity[10,11]. Thus, individuals with a monophasic curve have lower insulin clearance and relative muscle insulin resistance.

In contrast, individuals with a biphasic curve have high insulin sensitivity and insulin clearance. Accordingly, in individuals with a biphasic curve, the later rise in glucose levels could be due to enhanced insulin clearance, which contributes to preventing hypoglycemia through high muscle insulin sensitivity. A previous study showed that aerobic exercise for 1 year enhances muscle insulin sensitivity[12]; however, the glucose infusion rate during a glucose clamp did not increase as anticipated, because aerobic exercise increased MCRI by 87% and reduced steady-state serum insulin, suggesting that enhanced insulin clearance could compensate for higher insulin sensitivity.

The mechanisms underlying reduced insulin clearance in the monophasic group remain unclear. In the Hispanic cohort, insulin clearance has been shown to be highly hereditary, and chromosomal loci associated with insulin clearance have been identified[13]. Thus, reduced insulin clearance might be genetically determined, at least partially. Modest visceral fat accumulation might also contribute to reduced insulin clearance, but it is also possible that resulting hyperinsulinemia as a result of reduced insulin clearance might simultaneously induce visceral fat accumulation and insulin resistance[5].

In conclusion, a monophasic curve during 75-g OGTT is associated with reduced insulin clearance, lower muscle insulin sensitivity and more visceral fat accumulation compared with a biphasic curve.

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DISCLOSURE

The authors declare no conflict of interest.

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