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SHORT REPORT

Characteristics associated with elevated 1-h plasma glucose levels during a 75-g oral glucose tolerance test in non-obese Japanese men

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Keywords
1-h plasma glucose levels, Insulinogenic index, Non-obese

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ABSTRACT

Elevated 1-h plasma glucose (1h-PG; ≥155 mg/dL) during an oral glucose tolerance test is a risk factor for type 2 diabetes. However, the metabolic characteristics of non-obese Asians with elevated 1h-PG are unknown. Thus, we studied 59 non-obese Japanese men with normal glucose tolerance. We divided study participants into the Low 1h-PG group (<155 mg/dL) and the High 1h-PG group (≥155 mg/dL). We compared the metabolic characteristics of the groups, including tissue-specific insulin sensitivity measured using a two-step hyperinsulinemic-euglycemic clamp. Insulinogenic index and adiponectin levels were significantly lower in the High 1h-PG group than in the Low 1h-PG group. Other characteristics, including insulin sensitivity, adiposity and ectopic fat accumulation, were similar between the groups. In conclusion, non-obese Japanese men with high 1h-PG have impaired early-phase insulin secretion and lower adiponectin levels. Insulin resistance and abnormal fat distribution were not evident in this population.

INTRODUCTION

Earlier identification of individuals at high risk for type 2 diabetes and subsequent intervention is an important strategy for preventing the onset of type 2 diabetes. Impaired fasting glucose and impaired glucose tolerance are recognized as risk factors for type 2 diabetes; however, longitudinal studies have shown that 50–60% of individuals who have these conditions do not progress to diabetes within approximately 10 years, and 30–40% of individuals with diabetes had normal glucose tolerance at approximately 10 years before the onset of diabetes[1]. Thus, more sensitive and specific risk factors are required to efficiently identify individuals at high risk of developing type 2 diabetes. Abdul-Ghani *et al.*[2] used the receiver operating characteristic curve and showed that a 1-h glucose level of ≥155 mg/dL during an oral glucose tolerance test (OGTT) is a threshold to predict future type 2 diabetes, and it was a better predictor of developing type 2 diabetes than fasting (≥100 mg/dL)[3] and 2-h glucose (≥140 mg/dL) levels[4]. Similar to individuals with impaired glucose tolerance, white individuals with elevated 1-h glucose levels are characterized by adiposity, insulin resistance and impaired -cell function[5]. Asians with elevated 1-h glucose levels are also at high risk for developing type 2 diabetes[6,7]. Given that non-obese (body mass index <25 kg/m^2) Asians commonly develop type 2 diabetes[8], the metabolic characteristics of Asians with elevated 1-h glucose levels during an OGTT have not yet been elucidated. In this context, we designed the present study to identify the characteristics of non-obese Japanese men with elevated 1-h glucose levels during an OGTT.

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METHODS

Participants

We studied non-diabetic Japanese men aged between 30 and 50 years with normal glucose tolerance and body mass index

of 23 to <25 kg/m^2 [9]. All participants gave written informed consent to participate in the study. The ethics committee of Juntendo University approved this study, and the study was carried out in accordance with the principles outlined in the Declaration of Helsinki.

Study design and measurements

This study was a subanalysis of the Sportology Center Core Study, a prospective observational study of non-obese Japanese individuals[9]. Briefly, we carried out the OGTT and calculated the insulinogenic index (Δinsulin30 / Δglucose30). We also measured intramyocellular lipid and intrahepatic lipid levels by using proton-magnetic resonance spectroscopy[10] and abdominal fat areas by using magnetic resonance imaging[9,11]. Next, study participants underwent two-step hyperinsulinemic-euglycemic clamp tests with glucose tracer ([6,6-$^2H_2$]glucose) to measure insulin sensitivity in muscle, liver and adipose tissue[9,12]. We set insulin infusion rates as 10 and 20 mU/m^2/min during the first step (0–180 min) and the second step (180–360 min), respectively.

Statistical analysis

We used IBM SPSS Statistics for Windows, version 25.0. (IBM Corp., Armonk, NY, USA) for the analyses. Data are presented as the mean ± standard deviation. Differences in characteristics between groups were assessed using Student's *t*-test. The correlations between parameters were assessed using the Pearson correlation coefficient, then multiple regression analysis was carried out. All statistical tests were two-sided, with a 5% significance level.

RESULTS

We divided study participants into two groups based on 1-h glucose levels. Participants with 1-h glucose levels <155 mg/dL were categorized into the Low 1-h group, and participants with ≥155 mg/dL were categorized into the High 1-h group. Figure 1 shows the glycemic response (Figure 1a) and insulin concentrations (Figure 1b) during an OGTT. The insulinogenic index was significantly lower in the High 1-h group compared with the Low 1-h group, whereas total areas under the curve for glucose and insulin were higher in the High 1-h group (Table 1).

Table 1 summarizes the clinical features of the two groups. Ectopic fat in muscle and liver, and fat distribution were comparable between the groups. However, high-molecular-weight (HMW) adiponectin was lower in the High 1-h group. Insulin sensitivity in muscle (rate of disappearance divided by steady-state serum insulin during the second step), liver (percentage reduction in endogenous glucose production during the first step) and adipose tissue (percentage free fatty acid suppression/insulin during the first step) were comparable between the groups. Other parameters were also comparable between the groups.

Single correlation analyses showed that insulinogenic index ($r = -0.38$, $P = 0.003$) and HMW adiponectin ($r = -0.38$, $P = 0.003$) were significantly correlated with glucose level at 60 min, respectively. In contrast, HMW adiponectin was not significantly correlated to insulinogenic index ($r = 0.082$, $P = 0.539$). By multiple regression analysis, insulinogenic index ($\beta = -0.452$, $P = 0.001$) and HMW adiponectin ($\beta = -0.329$, $P = 0.012$) were independently associated with 1-h glucose, whereas age ($\beta = -0.065$, $P = 0.59$), body mass index ($\beta = 0.028$, $P = 0.82$) and muscle insulin sensitivity ($\beta = -0.118$, $P = 0.39$) were not.

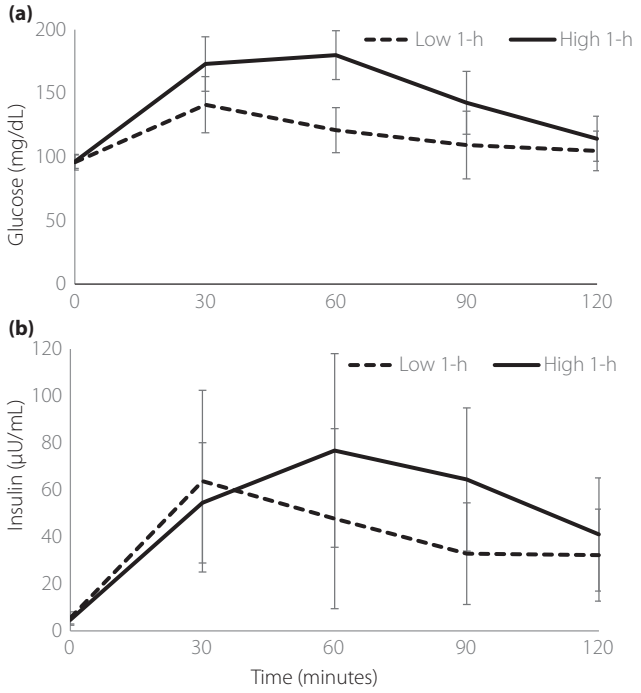

Figure 1 | (a) Plasma glucose and (b) insulin levels during oral glucose tolerance tests in participants with low 1-h (dashed lines) and high 1-h (solid lines) glucose. Data are reported as the mean ± standard deviation.

DISCUSSION

Although participants with high 1-h post-load plasma glucose levels are at high risk for type 2 diabetes, little is known about the metabolic characteristics of non-obese Asians with elevated 1-h glucose levels during an OGTT. The present study showed that the High 1-h group had a lower insulinogenic index, but similar insulin sensitivity and fat distribution compared with the Low 1-h group. However, the High 1-h group had lower HMW adiponectin levels than the Low 1-h group.

In the present study, as previously reported in white people[5], study participants with elevated 1-h glucose levels had an impaired insulinogenic index. A previous report suggested that early-phase insulin secretion is responsible for the postprandial glycemic response. For example, decreased early-phase insulin secretion is observed in individuals with impaired glucose tolerance and is associated with enhanced endogenous glucose production[13]. In addition, restoration of impaired early insulin

Table 1 | Clinical characteristics of the low 1-h and high 1-h groups

	Overall (n = 59)	Low 1-h (n = 29)	High 1-h (n = 30)	P
Age (years)	41.6 ± 5.3	41.3 ± 5.8	42.3 ± 4.9	0.49
BMI (kg/m^2)	24.0 ± 0.5	24.0 ± 0.5	23.9 ± 0.5	0.27
Fasting plasma glucose (mg/dL)	96.1 ± 5.7	95.8 ± 6.2	96.3 ± 5.2	0.77
Fasting serum insulin (μU/mL)	5.1 ± 2.5	5.5 ± 2.6	4.64 ± 2.3	0.19
Fasting serum C-peptide (ng/mL)	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	0.73
AUC glucose during OGTT (mg·min/dL·10^3)	16.1 ± 2.5	14.2 ± 1.4	18.0 ± 1.6	**<0.001**
AUC insulin during OGTT (μU·min/mL·10^3)	5.7 ± 2.9	4.9 ± 2.7	6.6 ± 2.9	**0.03**
Insulinogenic index	1.0 ± 0.9	1.4 ± 1.2	0.7 ± 0.3	**0.002**
Homeostatic model assessment for β-cell function (%)	61.9 ± 24.3	61.1 ± 18.9	62.6 ± 28.9	0.81
Matsuda index	7.5 ± 4.7	8.3 ± 5.0	6.7 ± 4.3	0.22
Free fatty acids (μEq/L)	565.8 ± 132.9	375.6 ± 115.8	401.9 ± 96.0	0.35
Triglycerides (mg/dL)	127.1 ± 94.1	134.8 ± 94.3	119.6 ± 94.9	0.54
HDL cholesterol (mg/dL)	59.9 ± 14.5	58.3 ± 13.8	61.5 ± 15.2	0.40
HbA1c (%)	4.9 ± 0.2	4.8 ± 0.2	4.9 ± 0.2	0.16
High-molecular-weight adiponectin (ng/mL)	1.4 ± 1.0	1.8 ± 1.2	1.1 ± 0.8	**0.02**
Intramyocellular lipid in TA (S-fat/Cre)	2.9 ± 1.6	3.0 ± 1.7	2.8 ± 1.4	0.63
Intramyocellular lipid in SOL (S-fat/Cre)	13.3 ± 6.0	12.6 ± 6.4	13.9 ± 5.6	0.43
Intrahepatic lipid (%)	2.9 ± 3.8	2.8 ± 4.1	3.1 ± 3.7	0.73
Abdominal visceral fat area (cm^2)	92.9 ± 31.8	85.2 ± 30.7	96.2 ± 36.7	0.22
Abdominal subcutaneous fat area (cm^2)	121.8 ± 37.1	120.9 ± 40.3	124.0 ± 38.3	0.76
VO_{2peak} (mL/kg per min)	32.3 ± 7.5	31.6 ± 6.2	33.1 ± 8.6	0.46
Daily physical activity (METs·h)	4.6 ± 1.3	4.6 ± 1.0	4.6 ± 1.5	0.97
%reduction in EGP during the first step (%/μU·mL^{-1})	65.9 ± 19.7	62.5±.20.2	69.2 ± 19.0	0.20
Rd/SS_{SI} during the second step (mg/kg FFM·min^{-1}·μU^{-1}·mL)	0.2 ± 0.1	0.2 ± 0.1	0.20 ± 0.1	0.97
%FFA suppression/insulin during the first step (%/μU·mL^{-1})	4.3 ± 1.4	4.25 ± 1.34	4.35 ± 1.5	0.79
MCRI during the second step (mL/min per m^2)	563.3 ± 103.5	541.7 ± 91.5	531.3 ± 115.0	0.70

Data are the mean ± standard deviation. P-values are based on Student's t-tests. The significant values are highlighted in bold. AUC, area under the curve; Cre, creatine; EGP, endogenous glucose production; FFM, fat-free mass; HbA1c, hemoglobin A1c; MCRI, metabolic clearance rate of insulin; MET, metabolic equivalent; OGTT, oral glucose tolerance test; Rd, rate of disappearance; S-fat, methylene signal intensity; SOL, soleus; SS_{SI}, steady-state serum insulin; TA, tibialis anterior; VO_{2peak}, peak oxygen consumption.

secretion by the insulin secretagogue, nateglinide, in patients with type 2 diabetes improves the glycemic response[14]. Given that insulin sensitivity was comparable between the groups, impaired early-phase insulin secretion might be the primary cause of postprandial hyperglycemia observed in the High 1-h group.

Unlike in white people[5], we did not find any differences in insulin sensitivity between the High and Low 1-h groups. Given that insulin resistance develops relatively in parallel with slight adiposity and ectopic fat accumulation in muscle and liver in non-obese Japanese indivuduals[9,15-18], insulin resistance could be an important risk factor for the onset of type 2 diabetes in Asians. Thus, impaired insulin secretion could be a more important risk factor for identifying susceptibility to type 2 diabetes in Asians.

In the present study, the High 1-h glucose group had lower HMW adiponectin levels than the Low 1-h group, and HMW adiponectin was significantly correlated with glucose level at 60 min. Lower adiponectin levels are often accompanied by adiposity, ectopic fat accumulation and insulin resistance[9,19], but those were comparable between the groups. One possible explanation is that the difference in adiponectin levels observed in the present study is too small to result in significant differences in insulin sensitivity. In contrast, it has been reported that adiponectin stimulates insulin secretion *in vivo* and *in vitro*[20], and a positive association between HMW adiponectin levels and insulin secretion was observed in a Japanese population-based study[21]. However, HMW adiponectin level was not significantly correlated with insulinogenic index in the present study. Thus, the underlying mechanism linking lower adiponectin level to elevated 1-h glucose is still unclear.

In conclusion, study participants with elevated 1-h glucose levels during an OGTT had a reduced early insulin secretion than participants with low 1-h glucose levels, but insulin sensitivity and fat distribution were comparable between the groups. Thus, in non-obese Japanese men, impaired early insulin secretion might be an underlying mechanism of elevated 1-h glucose levels during an OGTT.

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DISCLOSURE

The authors declare no conflict of interest.

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