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ORIGINAL PAPER

The interplay of insulin resistance and β-cell dysfunction involves the development of type 2 diabetes in Chinese obeses

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Abstract Type 2 diabetes mellitus (T2DM) is a heterogeneous disorder characterized by defects in insulin secretion and action and obesity plays an important role in the deterioration of glucose metabolism. In the present study we evaluated the degree of insulin resistance and first-phase insulin secretion of β-cell in obese subjects with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and T2DM in Chinese. A total of 220 subjects underwent standard 75 g oral glucose tolerance test (OGTT) and insulin-modified frequently sampled intravenous glucose tolerance test (FSIGT). Insulin sensitivity index (S_I) was assessed by the reduced sample number ($n = 12$) of Bergman's minimal model method with FSIGT. Insulin secretion capacities were determined by the insulinogenic index $(I_{30\ min} - I_{0\ min})/(G_{30\ min} - G_{0\ min})$ in OGTT and the acute insulin response to glucose (AIR) in FSIGT. The disposition index (DI), the product of AIR and S_I was used to determine whether AIR was adequate to compensate for insulin resistance. The S_I in healthy lean control group was significantly higher than that in NGT, IGT, and T2DM group, but there was no significant difference among NGT, IGT, and T2DM group. The AIR in NGT group was significantly greater than that in control group, but then it was progressively decreased in IGT and T2DM group. The value of DI in control group was significantly higher than that in those three abnormal groups, and was decreased from NGT to IGT and T2DM group with significant difference. It indicates that obese subjects with different glucose tolerances have a similar degree of insulin resistance but differ in insulin secretion in Chinese Han population.

Keywords Insulin resistance · Insulin secretion · Obesity · Impaired glucose tolerance · Diabetes

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Introduction

The development of type 2 diabetes mellitus is characterized by a progressive deterioration of glucose tolerance from normal glucose to impaired glucose tolerance and eventually to diabetes. Typically, this deterioration will last several years [1]. Defects in insulin action and insulin secretion are the major metabolic abnormalities underlying this progression [2]. In order to explore the relationship between these two factors, Bergman's minimal model of glucose kinetics, in conjunction with insulin-modified frequently sampled intravenous glucose tolerance test (FSIGT) became a good method, which provides one possible way to detect insulin sensitivity and β-cell secretory capacity, evaluated by SI (Index of insulin sensitivity) and AIR (Acute Insulin Response to glucose), respectively, at the same time. Now, it has been widely used in subjects with impaired glucose tolerance and type 2 diabetes mellitus in both clinical and epidemiological studies [3].

The general concept has continued to be challenged for a long time, that there could be racial or ethnic differences in the relative contributions of β-cell failure versus

decreased insulin sensitivity. Data from the Insulin Resistance Atherosclerosis Study (IRAS), which was a large multicenter epidemiological study of insulin sensitivity and cardiovascular risk in African-Americans, Hispanics, and non-Hispanic whites, had given some evidences. Such as, both non-diabetic African-Americans and Hispanics had increased insulin resistance and higher AIR than non-diabetic non-Hispanic whites [4]. But in type 2 DM, AIR was significantly higher only in African-Americans and there were no ethnic differences for insulin sensitivity [5]. There is still no data from China, which has one of the large populations in the world, of FSIGT as well. The purpose of this report is to determine whether insulin resistance and first-phase insulin secretion differ in Chinese Han obese with different glucose tolerances, including obesity with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and type 2 diabetes mellitus (T2DM).

Results

The demographics and characteristics of the 220 participants are presented in Table 1. No significant difference in age and gender was shown across the four groups. Body size measurements such as waist circumference, BMI, and waist to hip ratio (WHR) in healthy lean control group were significantly lower than those in NGT, IGT, and T2DM group, and there was no statistical difference in the latter three groups except that T2DM group had a greater WHR with significant difference ($p < 0.01$) as compared with NGT, IGT group. Figures 1 and 2 showed time courses of plasma glucose and serum insulin concentration during FSIGT, respectively.

Insulin resistance

As shown in Table 1, The $S_I \times 10^{-4}$ in control group (7.82 ± 2.97 l mU^{-1} min^{-1}) was significantly higher than that in NGT, IGT, and T2DM group (1.73 ± 1.14, 1.65 ± 1.09 and 1.64 ± 0.90 l mU^{-1} min^{-1}, $p < 0.001$), but there was no significant difference among NGT, IGT, and T2DM group (Table 2). It suggested that the obese patients with NGT, with IGT and even with T2DM all manifested a similar degree of insulin resistance. The results were the same after the S_I value was adjusted by age, BMI, and WHR.

Insulin secretion

Compared with the control group, the NGT obesity group had a greater insulin response to glucose challenge during OGTT and FSIGT expressed as $\Delta I_{30}/\Delta G_{30}$ and AIR, respectively, but the response was decreased significantly in the IGT group , yet the T2DM group showed an even lower insulin response to glucose than IGT group with significant difference ($p < 0.001$, Table 2). The disposition index was decreased from NGT to IGT and to diabetes with significant difference from one of each other ($p < 0.001$, Table 2). The results were the same after the AIR and DI values were adjusted by age, BMI, and WHR.

Table 1 General characteristics and laboratory parameters of NC, obesity with NGT, IGT, and type 2 DM

Items	Control ($n = 29$)	Obesity with NGT ($n = 63$)	Obesity with IGT ($n = 69$)	Obesity with T2DM ($n = 59$)
Sex (M/F)	13/16	29/34	33/36	28/31
Age (years)	37.1 ± 10.3	37.4 ± 11.1	36.6 ± 12.7	41.8 ± 14.2
BMI (kg/m^2)	20.7 ± 1.4	31.8 ± 4 .8***	30.2 ± 3.8***	29.8 ± 4.7***
WC (cm)	72.8 ± 5.5	97.7 ± 12.1***	92.7 ± 9.1***	96.8 ± 11.0***
WHR	0.81 ± 0.06	0.91 ± 0.07***	0.89 ± 0.07***	0.95 ± 0.08***$^{\#\Delta\Delta}$
SBP (mmHg)	112.2 ± 12.8	126.1 ± 18.7*	121.4 ± 16.5	130.0 ± 17.8**$^{\Delta}$
DBP (mmHg)	73.6 ± 7.0	82.22 ± 13.0*	80.5 ± 10.4*	84.9 ± 10.2***
TG (mmol/l)	0.87 ± 0.24	1.94 ± 1.00***	1.89 ± 1.13***	2.28 ± 1.82***
TC (mmol/l)	3.9 ± 0.9	5.0 ± 1.0***	5.0 ± 0.8***	5.1 ± 1.2***
HDL-c (mmol/l)	1.57 ± 0.25	1.27 ± 0.29*	1.25 ± 0.3**	1.15 ± 0.25**
LDL-c (mmol/l)	2.36 ± 0.50	2.95 ± 0.94	3.02 ± 0.76*	.3.04 ± 0.92
UA (mmol/l)	270 ± 57	357 ± 87**	336 ± 61*	331 ± 86

BMI: body mass index; WC: waist circumference; WHR: waist to hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: total triglycerides; TC: total cholesterol; UA: uric acid; Data are means ± SD

Compared with control, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Compared with obesity with NGT, $^{\#}p < 0.01$

Compared with obesity with IGT, $^{\Delta}p < 0.05$, $^{\Delta\Delta}p < 0.01$

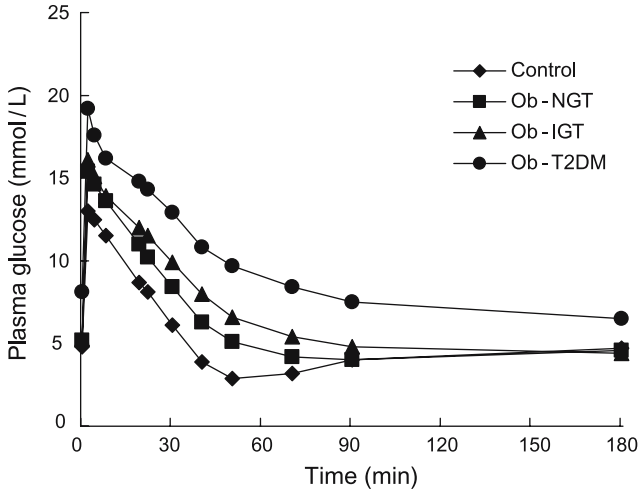

Fig. 1 Time courses of plasma glucose concentration during FSIGT

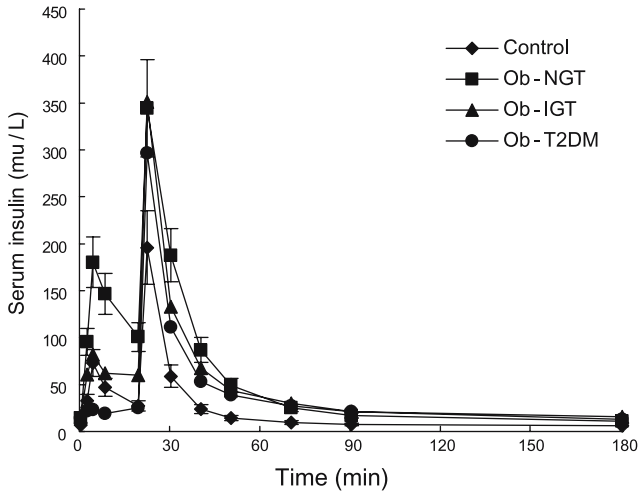

Fig. 2 Time courses of serum insulin concentration during FSIGT

The correlation between insulin sensitivity index (S_I) and other parameters

The correlation between insulin sensitivity index (S_I) and other parameters is shown in Table 3. The *p*-values from the multiple regression analyses with S_I as the dependent variable and waist circumference, BMI, WHR, 2-h glucose, fasting insulin, 2-h insulin, and triglyceride (TG), total cholesterol (TC), uric acid as independent variables demonstrated the significant correlations of S_I with waist circumference, 2-h insulin, 2-h blood glucose, and triglyceride.

The correlation between acute insulin response to glucose (AIR) and other parameters

The correlation between acute insulin response to glucose (AIR) and other parameters is shown in Table 4. The *p*-values from the multiple regression analyses with AIR as the dependent variable and age, fasting blood glucose, 2-h glucose, fasting insulin, 2-h insulin, and insulinogenic index as independent variables demonstrated that 2-h blood glucose, insulinogenic index, 2-h insulin, and age were significantly related to AIR.

Discussion

Though insulin resistance and β-cell function had been evaluated in either non-diabetic subjects or type 2 diabetic subjects, they were analyzed in different reports. This time, we used the Bergman's MINIMOD procedure, combined with 12-sample FSIGT, and with an infusion of exogenous insulin in the 20th minute, to cross-section compare SI and AIR among four groups of obesity with NGT, obesity with IGT, obesity with T2DM, and lean healthy controls. We observed that obesity with different glucose tolerances in Chinese Han population had a similar degree of insulin resistance. In response to the similar degree of insulin resistance, we found significant differences of acute insulin response to glucose challenge. In NGT group, we have seen a greater insulin response to glucose, and insulin secretion then decreased in IGT group. In T2DM group, the first-phase insulin release was blunted. Using the OGTT measurement of insulin secretion in terms of insulinogenic index we also found the same result.

The disposition index, usually calculated as the product of insulin sensitivity and insulin secretion, has been proposed as a measurement of the overall compensatory response of β-cell to insulin resistance [6]. Lower levels represent an inability of the pancreas to secret enough insulin at that level of insulin resistance. In our study, though there was an even higher AIR in obesity with NGT, once considering disposition index, our results demonstrated that even in obesity with NGT, the compensatory response of β-cell to insulin resistance is not sufficient, and in obesity with IGT, this index was markedly reduced, which in obesity with T2DM, the first-phase insulin secretion was essentially abolished.

No other ethnic group was recruited into our study. However, since the protocol of FSIGT was the same, we believe that the results of S_I and AIR were comparable among different studies. The S_I and AIR levels of our lean control were almost equal to that of the Western healthy volunteers (race not mentioned) [7] (S_I, 7.82 ± 2.97 vs. 7.10 ± 0.47; AIR, 389 ± 188 vs. 472.6 ± 37.0) , while BMI was much lower in Chinese (20.7 ± 1.4 vs. 26.2 ± 0.7). In obese non-diabetic group, Chinese has increased insulin sensitivity than African-Americans and Hispanics, but close to Non-Hispanic white [4] after adjusted for age, sex, BMI, and WHR (Chinese, 1.85 ± 0.19; African-Americans, 1.31 ± 0.134; Hispanics, 1.25 ± 0.11; Non-

Table 2 Insulin resistance and islet β-ell function evaluated by SI and AIR in obese with varying glucose tolerance

Items	Control (n = 29)	Obesity with NGT (n = 63)	Obesity with IGT (n = 69)	Obesity with T2DM (n = 59)
FPG (mmol/l)	4.8 ± 0.5	5.0 ± 0.5	5.3 ± 0.5**	8.9 ± 2.5$^{***\#\#\Delta\Delta\Delta}$
2 hPG (mmol/l)	5.2 ± 0.8	6.0 ± 1.0*	9.1 ± 0.9$^{***\#}$	15.1 ± 3.7$^{***\#\Delta}$
FINS (μU/ml)	7.4 ± 5.2	18.1 ± 14.1***	16.7 ± 9.3***	15.7 ± 11.0**
2 h Insulin (μU/ml)	24.4 ± 11.0	114.6 ± 89.2***	115.5 ± 53.7***	77.1 ± 64.8$^{***\Delta}$
$\Delta I_{30}/\Delta G_{30}$	13.1 ± 5.8	41.6 ± 28.0***	17.0 ± 13.8$^{\#}$	6.3 ± 5.8.$^{**\#\Delta}$
$S_I \times 10^{-4}$ (l mU^{-1} min^{-1})	7.82 ± 2.97	1.73 ± 1.14***	1.65 ± 1.09***	1.64 ± 0.90***
	7.02 ± 0.36	*1.85 ± 0.19***	*1.67 ± 0.18****	*1.81 ± 0.21****
AIR (mU l^{-1} min)	389 ± 188	1083 ± 848***	492 ± 358$^{\#}$	61 ± 96$^{***\#\Delta\Delta\Delta}$
	596 ± 124	*1037 ± 66****	*470 ± 61$^{\#}$*	*54 ± 70$^{***\#\Delta\Delta\Delta}$*
DI	2768 ± 1110	1576 ± 1115**	681 ± 561$^{***\#}$	66 ± 82$^{***\#\Delta\Delta\Delta}$
	2563 ± 197	*1590 ± 105***	658 ± 97$^{***\#}$	186 ± 115$^{***\#\Delta\Delta\Delta}$

FPG: fasting plasma glucose; 2hPG: 2 h blood glucose after glucose loading; FINS: fasting serum insulin; $\Delta I_{30}/\Delta G_{30} = (I_{30\ min} - I_{0\ min})/(G_{30\ min} - G_{0\ min})$; SI: insulin sensitivity index; AIR: acute insulin response to glucose; DI: deposition index. The italic data represented the values adjusted by age, BMI, and WHR

Compared with control, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

Compared with obesity with NGT, $^{\#}p < 0.01$, $^{\#\#}p < 0.001$

Compared with obesity with IGT, $^{\Delta}p < 0.05$, $^{\Delta\Delta\Delta}p < 0.001$

Table 3 The Spearman correlations between SI and other clinical parameters

	Age	WC	BMI	WHR	FPG	2hPG	AIR
r	–0.104	–0.549	–0.523	–0.4257	–0.109	–0.2419	–0.115
P	0.128	0.000	0.000	0.000	0.111	0.000	0.121
	FINS	2 h Insulin	TG	TC	HDL-c	LDL-c	Uric acid
r	–0.466	–0.460	–0.301	–0.193	0.092	–0.038	–0.330
P	0.000	0.000	0.000	0.010	0.243	0.632	0.000

The Spearman correlation coefficients were expressed by r-value. The relationship existed significantly when p-value > 0.05. WC: waist circumference; BMI: body mass index; WHR: waist to hip ratio; FPG: fasting plasma glucose; 2hPG: 2 h blood glucose after glucose loading; AIR: acute insulin response to glucose; FINS: fasting serum insulin; DI: deposition index; TG: total triglycerides; TC: total cholesterol

Table 4 The Spearman correlations between AIR and other clinical parameters

	Age	WC	BMI	WHR	FPG	2 h-glucose	FINS	2 h insulin	$\Delta I_{30}/\Delta G_{30}$
r	–0.252	0.040	0.186	–0.170	–0.686	–0.676	0.132	0.313	0.715
P	0.000	0.566	0.012	0.013	0.000	0.000	0.053	0.000	0.000

The Spearman correlation coefficients were expressed by r-value. The relationship existed significantly when p-value > 0.05. WC: waist circumference; BMI: body mass index; WHR: waist to hip ratio; FPG: fasting plasma glucose; 2hPG: 2 h blood glucose after glucose loading; FINS: fasting serum insulin; $\Delta I_{30}/\Delta G_{30} = (I_{30\ min} - I_{0\ min})/(G_{30\ min} - G_{0\ min})$

Hispanic white 1.60 ± 0.186). Significantly, obese and non-diabetic Chinese has much higher AIR than all the other groups (Chinese, 1037 ± 66; African-Americans, 358 ± 19; Hispanics, 363 ± 16; Non-Hispanic white 297 ± 12). The results of IRAS [5] showed that in newly diagnosed diabetic subjects, there were no significant ethnic differences in the proportion of insulin-sensitive subjects. Insulin sensitivity declined in each ethnic group as glucose tolerance worsened. Although subjects with IGT were less insulin sensitive than subjects with NGT, subjects with type 2 DM were less insulin sensitive than subjects with IGT. Different from this result, insulin resistance of Chinese diabetes keeps in the stage as low as that of obese non-diabetic subjects, no aggravation was found (SI Chinese, 1.81 ± 0.21; African-Americans 0.455 ± 0.060; Hispanics, 0.546 ± 0.123; Non-Hispanic white 0.707 ± 0.151). However, the AIR of Chinese in newly diagnosed diabetic subjects is similar to that of other groups.

(Chinese, 54 ± 70; African-Americans, 36 ± 11; Hispanics, 109 ± 23; Non-Hispanic white, 55 ± 25).

In this study, we observed that age did not seem to affect insulin resistance. This result is consistent with others. In European Group of Insulin Resistance [EGIR] study, Ferrannini and colleagues once found that after adjustment for BMI in 1,146 subjects, there was no effect of age on insulin sensitivity [8], while other studies had already demonstrated that aging was typically associated with diminished insulin sensitivity [9, 10]. The relationship between age and insulin secretion is still controversial. Absolute defects in acute insulin response to intravenous glucose related of age alone have not been clearly demonstrated, despite older subjects being glucose intolerant and insulin resistant compared with younger control subjects [11]. Fritsche et al. reported that aging is associated with deteriorating β-cell function and deteriorating proinsulin conversion to insulin [12]. In our present study we found that age is negatively correlated with AIR, and multiple regression analyses includes age as a predictor factor for AIR.

Meanwhile, in our present study, multiple regression analyses showed that insulin sensitivity index was negatively correlated with waist circumference, 2-h insulin and 2-h glucose, and triglyceride. It appears that adipose distribution is a more important determinant of insulin sensitivity than body size alone, because BMI does not account for the fact that people with similar BMI may have widely varying distribution of their adipose tissue. This finding is consistent with other studies. Fujimoto et al. demonstrated that BMI was not associated with insulin sensitivity but that the quantity of intra-abdominal fat was strongly related to the minimal model-derived measure of insulin sensitivity in Japanese Americans [13]. The relationship between obesity and β-cell function is still debatable. Kristina et al. found that intra-abdominal is most strongly correlated with β-cell dysfunction using FSIGT [14], yet the result from present study has not shown the correlation between WHR and AIR. In this report, multiple regression analyses showed AIR was positively correlated with insulinogenic index, and negatively correlated with 2 h-glucose and age. It seems reasonable that postprandial hyperglycemia could cause compensatory hypersecretion of insulin in IGT and the early stage of type 2 diabetes.

In conclusion, insulin resistance is similar in obese patients with different glucose tolerance in Chinese Han population but differs in first-phase insulin secretion. Significant β-cell hyper-function happens in non-diabetic obese. Reductions in both insulin sensitivity and beta cell function are present early in the course of the development of type 2 diabetes, even in the stage of IGT, and glucose intolerance is not associated with a further deterioration in insulin sensitivity. The different development of diabetes in Chinese from that of others races like African-Americans, Hispanics, and non-Hispanic whites needs more evidences to prove. Therapeutic approaches aimed at restoring a physiological pattern of insulin secretion could be beneficial to decreasing postprandial glucose in IGT and even in the early stage of type 2 diabetes mellitus. Likewise, to prevent the development of type 2 diabetes, obesity even with normal glucose tolerance should be treated as early as possible since the overall compensatory response of β-cell to insulin resistance, which has been demonstrated in the present study has been damaged.

Materials and methods

Subjects

The population studied consisted of 29 normal lean healthy control subjects with NGT (M/F = 13/16, aged 21–54, BMI 18.5–22.9 kg/m^2), 63 obesity with NGT (M/F = 29/34, aged 20–67, BMI 25.1–43.6 kg/m^2), 69 obesity with IGT (M/F = 33/36, aged 18–68, BMI 25.2–42.6 kg/m^2), and 59 obesity with T2DM (M/F = 28/31, aged 19–72, BMI 25.0–48.4 kg/m^2). We defined that all subjects were unrelated Chinese Han nationality living in Shanghai region and had normal renal, hepatic, and thyroid function. Normal controls and obese subjects with NGT had no family history of diabetes. Obesity with NGT, IGT, and T2DM patients were recently diagnosed and receiving dietary therapy alone. Women who were taking oral contraceptives were excluded. Menstruating women were studied during the follicular phase of their menstrual cycles. Before their participation, the nature, the purpose, and the possible risks of the study were explained to all subjects and gave informed consent. The study was approved by the Institutional Review Board of the Rui-Jin Hospital.

Methods

All subjects (n = 220) underwent a standard 75-g oral glucose tolerance test (OGTT) at their first visit and were classified as having NGT, IGT, or T2DM according to the criteria 1999 World Health Organization [15]. We defined impaired glucose tolerance (2-h postprandial plasma glucose ≥7.8 mmol/l and <11.1 mmol/l), and type 2 diabetes mellitus (fasting plasma glucose ≥7.0 mmol/l or 2-h postprandial plasma glucose ≥11.1 mmol/l). A fasting glucose level less than 6.1 mmol/l and a 2-h postprandial glucose level below 7.8 mmol/l were considered as normoglycemia. Lipid profile was collected after an overnight fast at

the first visit. Obesity was diagnosed as a BMI ≥ 25 kg/m^2 according to 2000 the Steering Committee of the Western Pacific Region of WHO criteria [16]. On the second visit day, all the subjects enrolled in this study (n = 220) underwent an insulin-modified FSIGT (OGTT and FSIGT were performed 3 days apart). None of the participants consumed alcohol, cigarette, and refrained from heavy physical exercise for at least 1 week before the test, and all subjects took diets containing at least 250 g carbohydrate for consecutive 3 days before the test.

Anthropometric measurements

Body weight was measured to the nearest 0.1 kg using a platform digital scale. Subjects were weighed light clothed without shoes, measurements of the waist at the smallest abdominal circumference and the hips at the largest gluteal circumference were used to determine upper versus lower body fat distribution by a same observer. Circumference measurements were performed twice and the mean value reported.

The reduced sample number (n = 12) of Bergman's minimal model method with FSIGT

After a 10-h overnight fast, a flexible catheter was inserted into each antecubital vein between 7 and 8 O'clock in the following morning for blood sampling and for glucose and insulin administration, respectively. Subjects were allowed to rest calmly for at least 15 min before blood sampling was begun. About 50% glucose (300 mg/kg) was administered intravenously within 2 min, blood samples were drawn frequently from the contralateral antecubital vein at 0, 2, 4, 8, 19, 22, 30, 40, 50, 70, 90, and 180 min after administration of glucose [17]. Enhancing the endogenous insulin response via administration of regular human insulin aimed to make the impact of insulin more recognizable and facilitated minimal model analysis at 20 min. Subjects received an *iv* bolus of regular human insulin 0.03 u/kg (Actrapid; Novo Nordisk) [18]. Serum was frozen at –20°C for subsequent analysis.

Laboratory analytic methods

Plasma glucose level was determined with a Beckman CX-7 automatic biochemical analyzer by the glucose oxidase method with intra-assay CV < 2.6%, inter-assay CV < 4.2%. Immunoreactive insulin level was measured in duplicate using a radioimmunoassy with intra-assay CV < 4.2%, inter-assay CV < 7.6% (Sangon Company, Shanghai, China). Serum total cholesterol and triglycerides were measured by the enzymatic method, and high-density lipoprotein (HDL) cholesterol was measured using specific precipitation method (Beckman LX-20, Brea, CA, USA).

Insulin resistance

Insulin resistance was determined from the insulin sensitivity index calculated from the insulin-modified FSIGT using the minimal model equations. S_I is the incremental change in insulin required to increase fractional glucose disappearance [17].

Insulin secretion

Insulinogenic index ($\Delta I_{30}/\Delta G_{30}$) was measured during the OGTT as the difference in insulin concentration between 30 and 0 min divided by the difference in glucose concentration between 30 and 0 min ($I_{30\ \mathrm{min}} - I_{0\ \mathrm{min}}$)/($G_{30\ \mathrm{min}} - G_{0\ \mathrm{min}}$). The acute insulin response to glucose (AIR) during FSIGT was calculated as the area under the insulin curve over basal concentration from 0 to 10 min [19]. The disposition index, which is the product of AIR and S_I was used to determine whether AIR was adequate to compensate for the degree of insulin resistance [19].

Statistical analysis

Analyses were performed using the SPSS 10.0 statistical packages. Results were expressed as mean ± SD. Variables not normally distributed were transformed by log or square root before analysis. The Spearman rank correlation coefficient was used to examine the relationship among the anthropometric measurements, the lipid, glucose and insulin level and S_I, AIR. Multiple regression analyses were performed separately with transformed S_I and AIR as dependent variables. Difference was considered significant if $p < 0.05$.

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