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ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 693–698
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Serum resistin level is associated with insulin sensitivity in Japanese patients with type 2 diabetes mellitus

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Received 28 August 2006; accepted 5 December 2006

Abstract

Impaired insulin secretion and decreased insulin sensitivity are the main pathophysiologic features responsible for development of hyperglycemia in type 2 diabetes mellitus. Insulin resistance is often associated with increased adipose tissue mass. To examine which variables influence insulin sensitivity, we compared metabolic parameters, serum resistin, leptin, and adiponectin concentrations to the insulin sensitivity, obtained by frequently sampled intravenous glucose tolerance test using the minimal model analysis, in 113 Japanese patients with type 2 diabetes mellitus. Duration of diabetes, fasting plasma glucose, fasting insulin, homeostasis model assessment of insulin resistance index, and serum resistin concentration were significantly higher in the insulin-resistant subgroup compared with the insulin-sensitive subgroup and correlated with insulin sensitivity. Stepwise regression analysis also identified these parameters as independent regulators of insulin sensitivity. The present study reconfirmed that fasting insulin level or homeostasis model assessment of insulin resistance would be a surrogate measure of insulin resistance and demonstrated that insulin resistance increases progressively after the onset of overt diabetes and that the serum resistin level is associated with insulin sensitivity, suggesting that resistin plays an important role in the development of insulin resistance in Japanese patients with type 2 diabetes mellitus.

1. Introduction

Type 2 diabetes mellitus usually results from an inadequate mass of functional pancreatic beta cells because of the lack of compensation to overcome insulin resistance. Although insufficiency of insulin secretion is thought to be a primary cause of type 2 diabetes mellitus in Japanese [1,2], variations in the genes involved in insulin action have been reported to be associated with type 2 diabetes mellitus [3-5], suggesting that insulin resistance is also an important factor for the development of type 2 diabetes mellitus in the Japanese population.

Insulin resistance is often associated with increased adipose tissue mass [6]. Adipocytes have been shown to be endocrine cells that secrete a variety of bioactive substances, so-called adipocytokines, including resistin, leptin, and adiponectin [7-9]. The mechanisms underlying insulin resistance are not fully clarified, but dysregulation of production and secretion of adipocytokines seems to be involved in the development of insulin resistance.

Resistin was identified by screening the genes that were induced during the differentiation of the adipocytes but were down-regulated in the mature adipocytes exposed to peroxisome proliferator–activated receptor γ ligands [10]. Recently, our coworkers discovered that the G/G genotype of resistin promoter single nucleotide polymorphism (SNP)-420 is associated with type 2 diabetes mellitus susceptibility [11] and that the SNP-420 genotype was a major determinant of serum resistin levels [12]. Resistin causes insulin resistance in rodents, although it remains controversial whether resistin levels correlate with insulin resistance in human subjects [13-17]. Leptin, secreted primarily from adipocytes, suppresses food intake and increases energy expenditure by enhancing thermogenesis and metabolic rate. Leptin also enhances insulin action in the liver, lowering

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0026-0495/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2006.12.019

hepatic glucose production [7,8]. However, in obesity, leptin levels are increased with adiposity, indicating that obese subjects may develop leptin resistance. Therefore, it is questionable that plasma leptin concentration correlates with insulin sensitivity in diabetic subjects. Adiponectin is an anti-inflammatory and antiatherogenic hormone exclusively synthesized in adipose tissue. Adiponectin appears to increase insulin sensitivity by regulating glucose and lipid metabolism in both liver and skeletal muscle [9,18].

Previously, we proposed a combined method using a 2-compartment model of C-peptide kinetics and minimal model analysis by frequently sampled intravenous glucose tolerance test (FSIGT) to assess beta cell function, insulin sensitivity, and insulin-independent glucose disposal [19-22]. In the present study, using this method, we examined the correlation of adipocytokines and metabolic parameters with insulin sensitivity in Japanese type 2 diabetic patients.

2. Subjects and methods

2.1. Subjects

We recruited 113 (77 men, 36 women) subjects with type 2 diabetes mellitus at the Diabetes Center, Chiba Central Medical Center, Chiba, Japan. All the subjects enrolled in this study were ethnic Japanese. Diabetes mellitus was diagnosed according to the 1985 World Health Organization criteria [23]. All patients tested negative for anti–glutamic acid decarboxylase and anti–tyrosine phosphatase–related protein (IA2) antibodies. Before participation, the purpose and risks of the study were explained, and informed consent was obtained from all the participants. The protocol was approved by the ethics committee of Chiba Central Medical Center.

2.2. Measurement of serum resistin, adiponectin, and leptin levels

Blood sampling was performed in fasting condition. Serum resistin concentration was measured by using a human resistin enzyme-linked immunosorbent assay kit (Linco Research, St Charles, MO). Serum leptin and adiponectin concentrations were measured with a radioimmunoassay kit (Linco Research).

2.3. C-peptide secretion rate and minimal model analysis

To examine the reserve of insulin secretion, insulin sensitivity, and glucose effectiveness, a combined method using a 2-compartment model of C-peptide kinetics and a minimal model approach in FSIGT was performed according to the protocol described before [22]. Briefly, after 10 to 12 hours overnight fast, a bolus of 50% glucose (25 g) was injected over 1 minute from the antecubital vein at time zero. Regular human insulin (0.05 U/kg; Humulin R, Lilly, Indianapolis, IN) dissolved in 5 mL of 0.9% normal saline was infused over 30 seconds at time 20 minutes. Blood samples were collected at −5, 0, 2, 3, 5, 7, 10, 15, 20, 22, 23, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, and 150 minutes for the determination of plasma glucose and insulin concentrations. C-peptide concentrations were measured at −5, 0, 2, 3, 5, 7, 10, 15, and 20 minutes. C-peptide secretion rate was mathematically estimated from serum C-peptide levels by deconvolution with a 2-compartment model for C-peptide disappearance kinetics. The first-phase C-peptide secretion rate (CS1) was determined by the sum of the C-peptide secretion rate from 0 to 5 minutes after intravenous glucose load. CS1 is 6.8 to 18.5 ng/mL per 5 minutes (10.8 ± 3.9) in subjects with normal glucose tolerance without diabetic patients in their family. Insulin sensitivity index (S_i) and glucose effectiveness (S_g) were calculated using the glucose and insulin concentrations by the minimal model software program, which we developed according to the algorithm described by Pacini and Bergman [20]. S_i and S_g are 2.6 to 7.6 × 10^{-4} min^{-1} μU^{-1} mL^{-1} (4.59 ± 1.76) and 1.15 to 4.1 × 10^{-2}/min (2.56 ± 0.92), respectively, in subjects with normal glucose tolerance without diabetic patients in their family.

2.4. Statistical analysis

Data are means ± SD. Parameter S_i was log transformed because it was not normally distributed. The estimate of insulin resistance by homeostasis model assessment of insulin resistance (HOMA-IR) was calculated with the formula: fasting insulin (μU/mL) × fasting glucose (mg/dL)/405. To investigate the relationship between adipocytokines and insulin sensitivity, we divided the study subjects into insulin-sensitive ($\log[S_i \times 10^4] > 0.125$, ie, $S_i > 1.35 \times 10^{-4}$) and insulin-resistant ($\log[S_i \times 10^4] < 0.125$, ie, $Si < 1.35 \times 10^{-4}$) subgroups. The cutoff value ($\log[S_i \times 10^4] = 0.125$) was obtained by the mean value of $\log(S_i \times 10^4)$ in the total subjects. Comparisons between groups were performed by means of unpaired Student t test and simple χ^2 test. Spearman coefficient was used to examine correlations. Multiple regression analysis in a stepwise manner was carried out to identify independent regulators of insulin sensitivity. Statistical significance was defined as $P < .05$. The software package JMP version 6 (SAS Institute, Cary, NC) was used for all computations.

3. Results

3.1. Characteristics of the subjects

Table 1 summarizes the clinical characteristics, measures of variables obtained in FSIGT, and adipocytokine concentrations in diabetic subjects. First-phase C-peptide secretion rate in FSIGT was extremely low in most diabetic subjects in this study (range, 0.034 to 7.127 ng/mL per 5 minutes) compared with the reference range in the subjects with normal glucose tolerance. CS1 values were less than 6.8 ng/mL per 5 minutes in 132 (99.2%) subjects and less than 2.0 ng/mL per 5 minutes in 96 (84.9%) subjects. In contrast, S_i and S_g values in diabetic subjects were

Table 1
Clinical characteristics, measures of variables obtained in FSIGT and adipocytokine concentrations, and comparison of these parameters between insulin-sensitive and insulin-resistant subgroups

	Total	Insulin sensitive, $\log(S_i \times 10^4) > 0.125$	Insulin resistant, $\log(S_i \times 10^4) < 0.125$
No. of patients	113	65	48
Female/male	36/77	16/49	20/28
Age (y)	55.8 ± 13.0 (19-88)	54.9 ± 11.7	57.2 ± 14.5
Onset age (y)	48.5 ± 12.8 (15-78)	49.5 ± 11.9	47.0 ± 13.9
Duration (y)	7.38 ± 8.19 (0-40)	5.36 ± 6.08	10.11 ± 9.81*
BMI (kg/m^2)	24.7 ± 3.88 (16.2-38.9)	24.1 ± 3.70	25.6 ± 4.01
HbA_{1c} (%)	7.62 ± 1.73 (4.8-13.9)	7.23 ± 1.87	8.14 ± 1.37*
Treatment (diet/OHA/insulin)	49/52/31	32/20/13	11/19/18*
FPG (mg/dL)	149.1 ± 44.1 (71-268)	139.4 ± 42.1	162.2 ± 43.8*
IRI (μU/mL)	9.70 ± 9.67 (2-63)	7.44 ± 7.69	12.7 ± 11.21*
HOMA-IR	3.82 ± 5.16 (0.48-35.0)	2.61 ± 4.30	5.47 ± 5.70*
CS1 (ng/mL per 5 min)	1.16 ± 1.06 (0.034-7.12)	1.28 ± 1.31	1.01 ± 0.67
Si ($\times 10^{-4}$ min^{-1} μU^{-1} mL^{-1})	2.30 ± 2.15 (0.032-9.17)	3.56 ± 2.04	0.59 ± 0.36*
$\log(S_i \times 10^4)$	0.125 ± 0.53 (−1.49-0.96)	0.49 ± 0.22	−0.36 ± 0.42*
S_g ($\times 10^{-2}$/min)	1.72 ± 0.91 (0-5.03)	1.60 ± 0.98	1.88 ± 0.79
TC (mg/dL)	203.3 ± 38.4 (124-309)	202.1 ± 33.4	205.0 ± 44.6
LDL (mg/dL)	121.0 ± 35.0 (40-230)	118.1 ± 34.2	125.0 ± 36.1
HDL (mg/dL)	55.8 ± 14.7 (32-123)	57.5 ± 15.3	53.5 ± 13.7
TG (mg/dL)	165.3 ± 123.8 (38-803)	166.5 ± 113.2	163.8 ± 138.1
Resistin (ng/dL)	10.35 ± 6.30 (2.7-32.5)	9.23 ± 6.05	11.8 ± 6.37*
Leptin (ng/dL)	5.15 ± 3.72 (1.4-24.7)	4.67 ± 3.61	5.79 ± 3.82
Adiponectin (μg/mL)	8.04 ± 4.87 (2.15-30.1)	8.35 ± 5.08	7.63 ± 4.60

Data are means ± SD. IRI indicates fasting insulin.
* $P < .05$ vs insulin-sensitive subgroup.

distributed in a wide range ([0.0323-9.17] $\times 10^{-4}$ min^{-1} μU^{-1} mL^{-1} for Si and [0-5.03] $\times 10^{-2}$/min for S_g).

3.2. Comparison of clinical features and adipocytokine concentrations between insulin-sensitive and -resistant subgroups

As shown in Table 1, all subjects were divided into 2 groups with regard to the value of S_i: an insulin sensitive group including 65 subjects and an insulin-resistant group including 48 subjects. The insulin-resistant group had significant increases in duration ($P = .004$), hemoglobin A_{1c} (HbA_{1c}) ($P = .0035$), fasting glucose ($P = .0066$), fasting insulin level ($P = .0058$), HOMA-IR ($P = .0049$), and resistin level ($P = .028$). There were no significant differences in age, onset age, body mass index (BMI), CS1, S_g, leptin and adiponecctin levels, total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride (TG) levels.

Table 2
Correlation of insulin sensitivity (log S_i) to clinical characteristics and measures of variables obtained in FSIGT (Spearman correlation coefficient)

	Log S_i	
	r	P
Age	−0.1638	.0831
BMI	−0.2377	.0112
Onset age	0.0323	.7342
Duration	−0.2483	.0080[a]
HbA_{1c}	−0.2333	.0129[a]
FPG	−0.2514	.0072[a]
IRI	−0.4735	<.0001[a]
HOMA-IR	−0.5046	<.0001[a]
CS1	−0.0258	.7865
S_g	−0.1666	.0778
TC	−0.0949	.3174
LDL	−0.1115	.2395
HDL	0.1765	.0614
TG	0.0409	.6672
Resistin	−0.300	.0012[a]
Leptin	−0.319	.0006[a]
Adiponectin	0.098	.297

[a] Significant correlation.

3.3. Correlation of insulin sensitivity to measures of variables

Insulin sensitivity (log S_i) had a strong negative correlation with fasting insulin level and HOMA-IR and moderate negative correlation with resistin and leptin concentrations. BMI, duration of diabetes, HbA_{1c}, and fasting plasma glucose (FPG) were also inversely associated

Table 3
Stepwise linear regression of independent variables associated with insulin sensitivity

Independent variables	Parameter estimate	SE	P
Intercept	0.7620	0.1277	<.0001
Sex (female/male)	−0.1434	0.0467	.0027
Duration	−0.01827	0.00538	.0010
IRI	−0.01314	0.00481	.0074
S_g	−0.1533	0.0483	.0020
Resistin	−0.01566	0.00755	.0406

Independent variables: sex, age, onset age, duration of diabetes, BMI, HbA_{1c}, FPG, IRI, CS1, S_g, resistin, leptin, adiponectin concentrations, TC, LDL cholesterol, HDL cholesterol, and TGs; 0.10 significance level for entry of variables into the model. Dependent variable = $\log(S_i \times 10^4)$. $R^2 = 0.309$.

Table 4
Correlation of adipocytokine concentrations with clinical characteristics and measures of variables obtained in FSIGT (Spearman correlation coefficient)

	Resistin		Leptin		Adiponectin	
	r	*P*	r	*P*	r	*P*
Age	0.2102	.0254[a]	0.0931	.326	0.3552	.0001[a]
BMI	0.240	.0104[a]	0.525	<.0001[a]	−0.229	.0146[a]
Onset age	0.0562	.554	0.0874	.357	0.2577	.0058[a]
Duration	0.1838	.0513	0.0096	.919	0.1279	.177
HbA_{1c}	0.0522	.583	−0.0425	.654	0.0074	.937
FPG	0.0431	.650	−0.0902	.342	0.0001	.999
IRI	0.342	.0002[a]	0.605	<.0001[a]	−0.161	.086
HOMA-IR	0.302	.0011[a]	0.530	<.0001[a]	−0.142	.133
CS1	0.203	.030[a]	0.249	.0077[a]	−0.264	.0206[a]
Log Si	−0.300	.0012[a]	−0.319	.0006[a]	0.098	.297
S_g	−0.194	.039[a]	−0.045	.634	−0.244	.0091[a]
TC	−0.0112	.906	0.0669	.481	−0.0787	.407
LDL	0.0400	.673	0.221	.0183[a]	−0.0257	.787
HDL	−0.167	.0764	−0.215	.0218[a]	0.299	.0013[a]
TG	0.0487	.608	0.0554	.560	−0.289	.0018[a]
Resistin			0.327	.0004[a]	0.0601	.527
Leptin					−0.0415	.662

[a] Significant correlation.

with insulin sensitivity (Table 2). Upon stepwise linear regression analysis with insulin sensitivity (log S_i) as a dependent parameter, sex, duration of diabetes, fasting insulin level, S_g, and resistin concentration remained as predictors, explaining 30.9% of insulin sensitivity (Table 3).

3.4. Correlation among the variables

Among the variables, strong correlations were seen between HbA_{1c} and duration ($r = 0.348$, $P = .0002$), fasting insulin and BMI ($r = 0.550$, $P < .0001$), CS1 and HbA_{1c} ($r = -0.309$, $P = .0008$), CS1 and FPG ($r = -0.379$, $P < .0001$), TC and LDL cholesterol ($r = 0.8155$, $P < .0001$), HDL cholesterol and BMI ($r = -0.352$, $P = .0001$), and HDL cholesterol and fasting insulin ($r = -0.375$, $P < .0001$).

3.5. Correlation of adipocytokines with measures of variables

Resistin concentration had a strong positive correlation with fasting insulin level and HOMA-IR and a strong negative correlation with log S_i (Table 4). Leptin concentration had a strong positive correlation with BMI, fasting insulin level, HOMA-IR, and resistin concentration, and a strong negative correlation with log S_i. Adiponectin concentration had a strong positive correlation with age and HDL cholesterol and a strong negative correlation with TGs.

4. Discussion

The present study revealed that insulin sensitivity (log S_i) had a strong negative correlation with fasting insulin concentration and HOMA-IR. HOMA-IR is calculated from the product of FPG and fasting insulin concentration. When used in place of FPG and fasting insulin as an independent variable in stepwise regression analysis, HOMA-IR remained as a predictor of insulin sensitivity (data not shown). For the subjects on insulin therapy, no correlation was observed between insulin sensitivity (log S_i) and fasting insulin ($r = -0.275$, $P = .134$) or HOMA-IR ($r = -0.350$, $P = .053$), indicating that it is not relevant to use fasting insulin or HOMA-IR as a surrogate measure of insulin resistance for insulin users. For the patients on diet therapy or oral hypoglycemic agent (OHA) treatment, a strong correlation was observed between insulin sensitivity (log S_i) and fasting insulin ($r = -0.488$, $P < .0001$) or HOMA-IR ($r = -0.515$, $P < .0001$), indicating fasting insulin or HOMA-IR is a surrogate measure of insulin resistance in the patients treated with diet or OHA, such as sulfonylureas, consistent with the previous report [24].

Insulin sensitivity (log S_i) and BMI were strongly correlated with leptin concentration in this study, consistent with previous reports demonstrating that leptin levels have a direct correlation with body fat, especially with subcutaneous fat area [25,26]. Although leptin has a favorable effect on insulin function and glucose metabolism, leptin levels are increased with fat mass, probably because of leptin resistance [7,8]. Thus, leptin level seems to be a marker of adiposity and obesity-related insulin resistance.

In this study, adiponectin concentration was positively correlated with HDL cholesterol and negatively correlated with BMI and TGs, whereas no significant correlation was observed between adiponectin concentration and insulin sensitivity (log S_i). Previous works revealed adiponectin levels are decreased in obesity under conditions of insulin resistance and diabetes [27,28]. Yatagai et al [25] demonstrated that insulin resistance (log S_i) was negatively correlated with serum adiponectin level and that visceral fat area was a predominant determinant of serum adiponectin level in Japanese patients with well-controlled

diabetes. Because the present study included patients with a more advanced stage of diabetes than those in previous studies, the contribution of adiponectin to insulin sensitivity may have become smaller as the disease progressed.

In the present study, insulin sensitivity (log S_i) was negatively correlated to the resistin concentration, and stepwise regression analysis revealed that resistin concentration was one of the independent determinants for insulin sensitivity in patients with type 2 diabetes mellitus. Recently, Osawa et al [12] found that fasting serum resistin concentration was higher in Japanese patients with type 2 diabetes mellitus compared with the subjects with normal glucose tolerance, and that logistic regression analysis showed serum resistin level was an independent factor of type 2 diabetes mellitus. In rodents, chronic elevation of serum resistin level was achieved by targeted overexpression of resistin in liver [29], by implantation of transfected 3T3-L1 cells into nude mice [30], or by adenovirus-mediated overexpression [31]. All these models showed significant impaired glucose tolerance and insulin signaling, along with hyperinsulinemia and dyslipidemia. Our present data and these previous reports suggest resistin plays a role in the increase of insulin resistance during the development of type 2 diabetes mellitus.

In contrast to the present study, some previous studies on Caucasians demonstrated no correlation between serum resistin level and S_i or HOMA-IR [16,17]. This discrepancy is probably due to the difference in ethnicity, because the pathogenesis of diabetes and clinical features of the patients seem different between Japanese and Whites. Japanese subjects with type 2 diabetes mellitus are usually nonobese but are composed of individuals with varied degrees of insulin sensitivity [1,2,28,32], consistent with the present work. Previous study showed that defective insulin secretion plays a predominant role in the nonobese subtype of diabetes, whereas both insulin resistance and insulin secretory defect are important in the obese subtype for the development of diabetes [2]. In contrast, insulin resistance seems to play a more important role in the development of diabetes in Caucasians [33]. The present study suggests that the insulin resistance in Japanese patients with type 2 diabetes mellitus is partially explained by the involvement of resistin among 3 kinds of adipocytokines examined, although the biochemical basis for insulin resistance in each ethnic group is still far from clear.

Accordingly, resistin may be a key molecule for the development of insulin resistance; thus, serum resistin level could be a good marker to detect insulin resistance as well as fasting insulin level or HOMA-IR index in Japanese patients with type 2 diabetes mellitus. Clinically, it is very important to assess the insulin sensitivity because insulin resistance often becomes an obstacle to the treatment of Japanese patients who have underlying beta cell dysfunction in most cases. In addition, in diabetic patients, serum resistin level reportedly correlates with inflammatory markers and is even predictive of the development of cardiovascular disease [34,35]. Therefore, determination of the serum resistin level would provide us with information about the pathophysiology of diabetes and the risk of the progression of atherosclerosis, leading to effective treatment for better glycemic control and prevention of cardiovascular events [36].

Significant increase in duration of diabetes was observed in the insulin-resistant subgroup compared with the insulin-sensitive subgroup, and duration was correlated with insulin resistance and was an independent determinant of insulin sensitivity, implying that insulin action tends to deteriorate progressively after development of overt diabetes. This finding may be supported by the previous observation that chronic hyperglycemia impairs insulin signaling [37].

In conclusion, the present study reconfirmed that fasting insulin level or HOMA-IR would be a surrogate measure of insulin resistance in patients treated without insulin and demonstrated that insulin resistance increases progressively after the onset of overt diabetes. The serum resistin level was inversely associated with insulin sensitivity and its independent determinant, suggesting that serum resistin plays an important role in the development of insulin resistance in Japanese patients with type 2 diabetes mellitus, although the ethnic difference in the pathogenesis of insulin resistance remains to be investigated.

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