

Roles of adipocyte derived hormone adiponectin and resistin in insulin resistance of type 2 diabetes

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Abstract

AIM: To detect plasma levels of new adipocyte derived hormone adiponectin and resistin in type 2 diabetes patients and to explore their potential roles in insulin resistance in type 2 diabetes.

METHODS: According to the body mass index (BMI), 60 type 2 diabetes patients were divided into two groups, one group was non-obese diabetes patients with BMI < 25Kg/M² (30 cases) and the other group was obese diabetes patients with BMI > 25Kg/M² (30 cases). There were 28 healthy persons in the control group. ELISA technique was employed to determine the plasma adiponectin and resistin concentrations. The fasting blood glucose, insulin and blood lipid were detected respectively by electrocheminescence immunoassay and immunoturbidimetric assay. Insulin resistance index and insulin sensitive index were calculated by the homeostasis model assessment (HOMO).

RESULTS: The levels of plasma adiponectin were decreased significantly in diabetes group compared to that in control group (non-obese: 8.58±0.86, obese: 6.22±1.34 vs 10.53±1.47 $P < 0.05$); moreover, adiponectin concentration in obese diabetes group was significantly decreased compared to that in non-obese diabetes group (6.22±1.34 vs 8.58±0.86, $P < 0.05$). The levels of plasma resistin were increased significantly in diabetes group compared to that in control group (obese: 18.64±4.65, non-obese: 24.05±9.07 vs 14.16±5.25, $P < 0.05$);

furthermore, the levels of resistin in obese diabetes group were increased significantly compared to that in non-obese diabetes group ($P < 0.05$). Plasma adiponectin was correlated negatively with BMI, blood glucose, insulin resistance index and triglyceride (respectively, $r = -0.55$, $P < 0.01$; $r = -0.51$, $P < 0.05$; $r = -0.52$, $P < 0.05$; $r = -0.39$, $P < 0.05$), while it was positively correlated with insulin sensitive index ($r = 0.45$, $P < 0.05$). Conversely, plasma resistin correlated positively with BMI, blood glucose, triglyceride and insulin resistance index (respectively, $r = 0.40$, $P < 0.05$; $r = 0.52$, $P < 0.05$; $r = 0.46$, $P < 0.01$; $r = 0.27$, $P < 0.05$), and negatively correlated with insulin sensitive index ($r = -0.32$, $P < 0.05$).

CONCLUSION: Plasma adiponectin and resistin are associated with the disorder of metabolism of glucose and lipid in diabetes. The relationship between these hormone and insulin sensitivity suggests that they may take part in the development of insulin resistance of type 2 diabetes.

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Key words: Adiponectin; Resistin; Adipocyte; Type 2 diabetes

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INTRODUCTION

The prevalence of obesity is rapidly increasing with the changes of life style and structure of meals. The high prevalence of obesity has led to an increase in medical conditions that accompany obesity, especially type 2 diabetes (also known as non-insulin dependent diabetes mellitus, NIDDM), hypertension, cardiovascular disease (CVD), and certain cancers. Perhaps most importantly, obesity generally confers a significantly increased rate of mortality when compared with individuals of normal body weight^[1].

Adipose tissue was once considered to be an inert storing depot for energy, in the form of triglyceride. However, in recent years, a line of evidence has

Table 1 Subject characteristics and plasma glucose, insulin, and lipid levels

Parameter	Control group	Non-obese diabetes group	Obese diabetes group
<i>n</i>	28	30	30
Age (yr)	47±11	48±8	52±9
Gender (M/F)	14/14	14/16	16/14
BMI (kg/m ²)	24.03±4.05	23.13±1.62	27.25±1.71 ^{ac}
FPG (mmol/L)	4.97±0.56	9.9±2.03 ^a	10.03±2.08 ^a
FINS (mU/L)	6.25±4.22	9.52±7.81	8.72±4.64
IR	0.50±0.35	0.98±0.59 ^a	1.22±0.53 ^a
ISI	-3.61±0.35	-4.09±0.59 ^a	-4.33±0.54 ^a
TCH (mmol/L)	4.79±1.07	5.79±1.42 ^a	5.61±1.79 ^a
TG (mmol/L)	1.48±1.74	2.45±1.46 ^a	3.05±1.92 ^a
NEFA (mmol/L)	0.71±0.18	0.95±0.21 ^a	1.13±0.24 ^a

BMI: body mass index; FPG: fasting plasma glucose; FINS: fasting insulin; IR: insulin resistance; ISI: insulin sensitive index; TCH: total cholesterol; TG: plasma triglyceride; NEFA: non-esterified fatty acids. ^a*P*<0.05 vs control group; ^b*P*<0.05 vs non-obese diabetes group.

demonstrated a much more complex function of adipose tissue, as an endocrine organ that releases hormones into the blood stream to take part in their potential implication in insulin resistance, obesity and diabetes^[2]. The recent boom of interest in adipocyte derived factors has resulted in identification of a large group of adipocyte specific proteins, such as adiponectin, acylation stimulating protein, resistin, leptin, etc^[3]. These adipocyte derived hormones are presently subject to intensive research concerning their involvement in the regulation of adipose tissue physiology, and in particular, their potential implication in insulin resistance, obesity and diabetes^[4].

Both adiponectin and resistin are new hormones secreted exclusively from adipose tissue. They have important biological activity on glucose and lipid metabolism; moreover, they can affect insulin resistance. The present study was carried out based on the hypothesis that plasma adiponectin and resistin would play some roles in type 2 diabetes.

MATERIALS AND METHODS

Subjects and fasting blood samples

A total of 88 subjects were recruited from outpatient clinics at the Tongji Medical Centre, Tongji Hospital, Wuhan, Hubei province, China. All participants gave informed consent and the study was approved by Tongji Hospital Ethics Committee. Type 2 diabetic patients (*n*=60) were recruited at the time of their initial screening at the Endocrinology Clinic. Non-diabetic control subjects (*n*=28) were normal healthy adults recruited at their yearly checkups. Diabetes was defined in conformity with 1999 World Health Organization. According to the obesity criteria established in 2000 of Asia area, the diabetes patients were divided into two groups: (1) Non-obese diabetes group: BMI < 25 (*n*=30); (2) Obese diabetes group: BMI ≥ 25 (*n*=30). The type 2 diabetic participants had not taken any medication (including antidiabetic medication or herbal preparations) before we collected the blood samples. Subjects in diabetic and control groups were confirmed to have no known disease (including cardiovascular disease, thyroid disease,

Table 2 Plasma adiponectin and resistin levels in diabetes patients divided by body weight

	Control group	Non-obese diabetes group	Obese diabetes group
Adiponectin (mg/L)	10.53±1.47	8.58±0.86 ^a	6.22±1.34 ^{ac}
Resistin (mg/L)	14.16±5.25	18.64±4.65 ^a	24.05±9.07 ^{ac}

^a*P*<0.05 vs control group; ^c*P*<0.05 vs non-obese diabetes group.

hypertension or any other acute and chronic disease condition) or any current infectious condition.

Blood samples were drawn after an overnight fast from an antecubital vein. Fasting plasma samples were used for measurement of all parameters. The samples were centrifuged, aliquoted and immediately frozen at -80°C for analyses of lipoproteins and proteins

Analytical procedures

Plasma samples were analyzed for concentrations of adiponectin, resistin, insulin, glucose, non-esterified fatty acids (NEFA), triglycerides (TG), total cholesterol (TCH). Plasma triglycerides (TG) were measured by GPO-PAP method and total cholesterol was measured by COD-PAP method. The plasma NEFA concentration was determined by colorimetric enzymatic assay (WAKO Chemicals, Tokyo, Japan).

Plasma glucose was determined by glucose-oxidase method (AVE-852 half-auto biochemical analyzer). Plasma insulin was measured by electrocheminescence immunoassay (Elecsys 1010, Roche Instrument Center AG).

Plasma adiponectin was measured by ELISA (B-Bridge International, Phoenix, AZ, USA) and plasma resistin also measured by ELISA (BioVendor Laboratory Medicine, USA).

Calculation

Body mass index (BMI) was calculated as weight (kg) per height (m²). Insulin resistance index (IRI) was calculated by homeostasis model assessment, HOMA-IR as (fasting insulin IU/L) × (fasting glucose mmol/L) / 22.5 as previously reported by Matthews^[5]. Insulin sensitivity index (ISI) was calculated as 1/[(fasting insulin IU/L) × (fasting glucose mmol/L)].

Statistical analysis

All results are displayed as mean ± SE (standard error of mean) unless stated otherwise. ANOVA analyses were used to compare means among the groups and correlations were calculated using Pearson correlation coefficient or multiple regression analysis. *P*<0.05 was considered statistically significant for all analyses.

RESULTS

The age and gender had no significant differences between diabetes group and control group. Subject characteristics are presented in Table 1.

The results of adiponectin and resistin are shown in

Table 3 Correlation analysis of fasting plasma adiponectin and resistin with the other parameters

Parameter	Adiponectin		Resistin	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
BMI	-0.55	0	0.4	0
FPG	-0.51	0	0.52	0
FINS	0.15	0.16	0.1	0.39
IR	-0.52	0	0.46	0
ISI	0.45	0	-0.32	0
TCH	-0.15	0	0.07	0.53
TG	-0.39	0.02	0.27	0.01
NEFA	-0.45	0	0.29	0

BMI: body mass index; FPG: fasting plasma glucose; FINS: fasting insulin; IR: insulin resistance; ISI: insulin sensitive index; TCH: total cholesterol; TG: plasma triglyceride; NEFA: non-esterified fatty acids. * $P < 0.05$ vs control group; † $P < 0.05$ vs non-obese diabetes group.

Table 2. There was a significant decrease in adiponectin in diabetes group as compared to that in control group ($P < 0.05$). Furthermore, adiponectin in obese diabetes group was lower than that in non-obese diabetes group ($P < 0.05$), while plasma resistin levels of non-obese diabetes group and obese diabetes group were apparently increased as compared to that in control group ($P < 0.05$). Moreover, resistin level of obese diabetes group was also apparently higher than that of non-obese diabetes group ($P < 0.05$).

There were significant differences in blood lipid parameters, including TG, TCH and NEFA, as given in Table 1. Cholesterol and triglyceride in non-obese diabetes group and obese diabetes group were apparently higher than that in control group ($P < 0.05$), but there was no significant difference between non-obese diabetes group and obese diabetes group. The level of fasting insulin was not significantly different among the three groups ($P > 0.05$). Fasting plasma glucose in diabetes group was apparently higher than that in control group ($P < 0.05$), and there was no significant difference between non-obese and obese diabetes groups.

Pearson correlation analysis was used to identify the factors that most closely related to the hormones adiponectin and resistin, as shown in Table 3. Plasma adiponectin correlated negatively with BMI, blood glucose, insulin resistance index and triglyceride (respectively, $r = -0.55$, $P < 0.05$; $r = -0.51$, $P < 0.05$; $r = -0.52$, $P < 0.05$; $r = -0.39$, $P < 0.05$); whereas it was positively correlated with insulin sensitive index ($r = 0.45$, $P < 0.05$). Plasma resistin was correlated positively with BMI ($r = 0.39$, $P < 0.05$), fasting plasma glucose ($r = 0.37$, $P < 0.05$) and triglyceride ($r = 0.41$, $P < 0.05$); and it was correlated positively with insulin resistance index ($r = 0.49$, $P < 0.05$), but negatively with insulin sensitive index ($r = -0.34$, $P < 0.05$). There was no significant correlation between plasma resistin and insulin and cholesterol, but there was significant correlation between plasma adiponectin and cholesterol ($r = -0.15$, $P < 0.05$).

DISCUSSION

Recent clinical and experimental data have radically modified the concept of adipose tissue as one solely

devoted to energy storage and release. Adipose tissue is also an important endocrine organ. It can release hormones into the blood stream in response to specific extra cellular stimuli or changes in metabolic status. The factors secreted by adipose tissue are actively involved in energy homeostasis in that they signal to the brain, the pancreatic β -cells, the liver and skeletal muscle in order to adapt to changes in energy stores by modulating feeding, insulin secretion and insulin sensitivity^[6]. Secreted factors may include leptin; steroids and glucocorticoids; peptide hormone precursors, e.g. angiotensinogen; complement factors, e.g. adipsin, acylation-stimulating protein (ASP) adiponectin; pro-inflammatory cytokines, e.g. tumor necrosis factor α (TNF- α), interleukin 6 (IL-6); resistin; etc. Most of these products probably act through paracrine or autocrine mechanisms^[7].

Adiponectin, also known as adipose most abundant gene transcript 1 (apM1), adipoQ and adipocyte complement related protein of 30 Kdaltons (ACRP30) was originally identified as the product of a highly induced gene after 3T3-L1 differentiation. It is a relatively abundant plasma protein (around 0.01% of total plasma proteins) that is exclusively synthesized and secreted by white adipose tissue (WAT)^[8]. Adiponectin has many metabolic actions involving peripheral tissue and the regulation of energy homeostasis, particularly energy expenditure. The new adipocytin can decrease plasma glucose, increase clearance of a glucose load and ameliorate insulin resistance in mouse models with normal (C57Bl/6J), reduced (ob/ob, db/db) or absent (lipotrophic mice) adiponectin pathways^[9]. Acute administration in mice reduces elevated postprandial NEFA resulting from ingestion of a high-fat test meal or lipid intravenous injection^[10]. Daily administration of adiponectin in mice on a high-fat/ high-sucrose diet induces marked and sustainable weight loss without affecting food intake^[11]. Adiponectin decreases muscle and liver TG content, increases gene expression related to muscle NEFA uptake and utilization, increases muscle NEFA oxidation, and enhances hepatic insulin-mediated suppression of glucose production^[12]. Adiponectin knockout mice demonstrate insulin resistance after a glucose load or after a high-fat/ high-sucrose diet (2 wk), delayed NEFA clearance and decreased expression of NEFA transporters in muscle^[13]. It is apparent that adiponectin is very important for the metabolism of lipid and glucose, as well as insulin sensitivity.

Adiponectin is the only WAT derived hormone whose levels are downregulated in obesity. Human, primate and mouse models of obesity and/or insulin resistance (Type II DM and ob/ob mice) have reduced circulating adiponectin concentrations and expression in WAT^[14]. In a recent study in adolescents, plasma adiponectin was shown to correlate with insulin sensitivity but was inversely proportional to plasma triglyceride and intra-myocellular lipid, suggesting its functional link to insulin resistance^[15]. During weight-reduction or prolonged negative energy balance, circulating adiponectin is elevated in human^[16]. We found that plasma adiponectin was decreased significantly in diabetes group, especially in obese diabetes group. Moreover, plasma adiponectin correlated negatively with insulin resistance

index, triglyceride and correlated positively with insulin sensitive index. It is well known that adiponectin improves insulin sensitivity of the whole body, so we speculated the decreased adiponectin in type 2 diabetes may be one of the reasons to cause insulin resistance. The change of plasma adiponectin was correlated with the development of insulin resistance in diabetes. It is unclear why adiponectin levels were decreased in obese diabetes with more fat tissue which can produce adiponectin. Some researchers speculated that the suppression of adiponectin production in obesity and diabetes may be mediated by an autocrine negative feedback inhibition in WAT, for instance, lower expression of adiponectin mRNA was found in cultured human visceral WAT and microarray study demonstrated that adiponectin expression is suppressed with the development of obesity and diabetes in mice^[17].

Resistin is another protein identified recently as a hormone secreted by adipocytes which leads to insulin resistance *in vivo* and *in vitro* and might therefore be an important link between obesity and diabetes^[18]. 3T3-L1 cells can secrete abundant resistin into the medium and its mRNA is induced (reduced?) markedly during adipocyte differentiation of 3T3-L1 cells^[19]. When these adipocytes were exposed to specific resistin antibody, the insulin-stimulated glucose uptake was increased significantly. Consistent with the results, treatment of 3T3-L1 adipocytes with purified resistin reduced insulin-stimulated glucose uptake^[20]. These studies suggest that resistin functions as a signal to decrease insulin-stimulated glucose uptake. Administration of anti-resistin antibody also can improve blood glucose and insulin action in mice with diet-induced obesity^[21]. Resistin gene and protein expression were increased in human abdominal adipose tissue. In this study we found that plasma resistin levels of non-obese diabetes group and obese diabetes group were apparently higher than that in control group. Furthermore, resistin levels in obese diabetes group were increased as compared to non-obese diabetes group. Meantime plasma resistin was correlated positively with insulin resistance index. Al-Harithy *et al*^[22] had similar result in their study on type 2 diabetes. It was well known that resistin levels were increased in differentiation of adipocytes, obesity and people on high fat diet?, and it is increased in abdominal vs. thigh adipose tissue. There is a potential link between central obesity and type 2 diabetes and/or cardiovascular disease^[23]. Functionally, resistin impairs glucose tolerance, insulin action, and increases hepatic glucose production, while a neutralizing antibody normalizes glucose levels and tissue glucose uptake^[24]. It suggests that increased plasma resistin may be correlated with the development of insulin resistance in type 2 diabetes.

Type 2 diabetes mellitus is characterized by target-tissue resistance to insulin. It is strongly linked to obesity as over 80% of sufferers are obese^[25]. While the molecular basis for this link has remained a mystery. Insulin resistance is the core pathogenic factor for diabetes. In addition, it is also strongly associated with obesity, hypertension and cardiovascular disease, etc. The new adipocytes derived hormones adiponectin and resistin may be an important link between increased fat mass and insulin resistance and disorder of metabolism of lipid and glucose in diabetes. Adipocytes have become the center for the study of the

association of insulin resistance and type 2 diabetes^[26]. Studies of the roles of adiponectin and resistin will shed new light on prevention and treatment of type 2 diabetes, and open a new field for the development of new drugs to improve insulin resistance.

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