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Interleukin 6, adiponectin, leptin, and insulin resistance in nonobese Japanese type 2 diabetic patients

Ataru Taniguchi[a,*], Mitsuo Fukushima[b], Michihiro Ohya[a], Yoshikatsu Nakai[c], Satoru Yoshii[a], Shoichiro Nagasaka[d], Kazunari Matsumoto[e], Yoshiro Taki[a], Akira Kuroe[a], Fusanori Nishimura[f], Yutaka Seino[a]

[a]*Division of Diabetes and Clinical Nutrition, Kansai-Denryoku Hospital, Osaka 553-0003, Japan*
[b]*Department of Health Informatics Research, Translational Research Informatics Center, Foundation for Biochemical Research and Innovation, Kobe 650-0047, Japan*
[c]*School of Health Sciences Faculty of Medicine, Kyoto University Graduate School of Medicine, Kyoto 606-8507, Japan*
[d]*Division of Endocrinology and Metabolism, Jichi Medical School, Tochigi 700-0045, Japan*
[e]*Diabetes Center, Sasebo Chuoh Hospital, Nagasaki 857-0044, Japan*
[f]*Department of Pathophysiology/Periodontal Science, Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan*

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Abstract

The aim of the present study was to investigate the relationships between interleukin 6 (IL-6) and insulin resistance, serum leptin, serum adiponectin, or serum lipids including triglycerides in 98 nonobese Japanese type 2 diabetic patients. Insulin resistance was estimated by the insulin resistance index of homeostasis model assessment (HOMA-IR). Serum IL-6 concentration was negatively correlated to high-density lipoprotein cholesterol ($r = -0.295$, $P = .004$), but was not associated with HOMA-IR ($r = 0.016$, $P = .871$), body mass index (BMI) ($r = 0.090$, $P = .375$), systolic ($r = 0.169$, $P = .116$) and diastolic ($r = -0.061$, $P = .570$) blood pressures, leptin ($r = 0.062$, $P = .544$), and adiponectin ($r = -0.020$, $P = .841$) in these patients. In contrast, serum leptin level was positively correlated to HOMA-IR ($r = 0.291$, $P = .004$), BMI ($r = 0.338$, $P < .001$), and systolic blood pressure ($r = 0.241$, $P = .025$). Serum adiponectin level was negatively correlated to HOMA-IR ($r = -0.288$, $P = .005$), BMI ($r = -0.308$, $P = .002$), diastolic blood pressure ($r = -0.269$, $P = .012$), and triglycerides ($r = -0.338$, $P < .001$), and positively correlated to high-density lipoprotein cholesterol ($r = 0.300$, $P = .003$) in our patients. From these results, it can be suggested that fasting serum IL-6 is not a major factor responsible for the evolution of insulin resistance in nonobese Japanese type 2 diabetic patients.

1. Introduction

Type 2 diabetes mellitus is a heterogeneous syndrome characterized by insulin resistance and/or defective insulin secretion [1]. The mechanisms underlying insulin resistance are not yet fully clarified. We previously demonstrated that body mass index (BMI) and serum triglycerides are the most important factors responsible for the evolution of insulin resistance in Japanese type 2 diabetic patients [2,3]. Thereafter, we showed that both leptin and adiponectin are correlated to insulin resistance in nonobese Japanese type 2 diabetic patients [4,5]. Serum triglyceride level is positively correlated with visceral fat area [6]. Serum leptin level is positively correlated to subcutaneous fat areas, whereas serum adiponectin level is negatively correlated to visceral fat areas [4,5]. Thus, the factors associated with insulin resistance in nonobese Japanese type 2 diabetic patients are hypothesized to be linked to adipose tissue–related insulin resistance.

Interleukin 6 (IL-6) is one of the candidates responsible for adipose tissue–related insulin resistance in man. Mohamed-Ali et al [7] are the first to show that a considerable portion of circulating IL-6 is derived from adipose tissue. Circulating levels of IL-6 have been reported to be high in obese people and in patients with type 2 diabetes mellitus [8-10]. Bastard et al [9] have shown that

* Corresponding author. Fax: +81 6 6458 6994.
E-mail address: taniguchi.ataru@a5.kepco.co.jp (A. Taniguchi).

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not only leptin but also IL-6 is associated with BMI and insulin resistance, and that IL-6 and leptin are interrelated in white obese type 2 diabetic patients. Haffner et al [10] demonstrated that serum levels of IL-6 were associated with BMI and insulin resistance in obese type 2 diabetic patients. However, obesity and insulin resistance are related to each other, and it remains to be elucidated whether the relationship between IL-6 and insulin resistance is independent of obesity in type 2 diabetic patients.

Nonobese Japanese type 2 diabetic patients are unique in that they are divided into 2 variants: one with insulin resistance and the other with normal insulin sensitivity [2,3,11,12]. Thus, the aim of the present study was to examine the relationship between fasting serum IL-6 level and insulin resistance in nonobese Japanese type 2 diabetic patients without confounding the effect of obesity.

2. Subjects and methods

Ninety-eight nonobese Japanese type 2 diabetic patients who visited Kansai-Denryoku Hospital were enrolled for the present study. Type 2 diabetes mellitus was diagnosed based on the World Health Organization criteria [13]. They had no evidence of current acute illness including clinically significant infectious diseases. The duration of diabetes was 11.1 ± 0.8 years (range, 1-35 years). Of 98 diabetic patients, 84 were taking sulfonylureas, and the rest were treated with diet alone. No patients had received insulin therapy. All subjects had ingested at least 150 g of carbohydrate for the 3 days preceding the study. None of the subjects had significant renal, hepatic, or cardiovascular disease. Patients did not consume alcohol or perform heavy exercises for at least 1 week before the study.

Blood was drawn in the morning after a 12-hour fast. Plasma glucose was measured with the glucose oxidase method. Triglycerides, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) were also measured. Serum insulin was measured using a 2-site immunoradiometric assay (Insulin Riabead II, Dainabot, Japan). Coefficients of variation were 4% for insulin higher than 25 μU/mL and 7% for insulin less than 25 μU/mL, respectively. Serum IL-6 was measured by enzyme-linked immunosorbent assay (Quantikine IL-6, R&D Systems, Oxford, UK). Serum leptin and adiponectin concentrations were measured with a radioimmunoassay kit (Linco Research, St Charles, MO) [4,5]. The intra- and interassay coefficients of variation were less than 5% for leptin and adiponectin. Samples for insulin, IL-6, leptin, and adiponectin were prepared, frozen, and stored at −70°C until the assay.

The estimate of insulin resistance by HOMA (HOMA-IR) was calculated with the formula: fasting serum insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5 [14]. The HOMA-IR value (mean ± SD) of healthy tolerant subjects was 1.6 ± 0.9, and we defined the values higher than 2.5 as an insulin-resistant state and the values less than 2.5 as an insulin-sensitive state [2,3]. The threshold value for insulin resistance (2.5) in our study is similar to that (2.77) in nonobese subjects with no metabolic disorders, reported by Bonora et al [15]. It may be argued that the use of sulfonylureas in patients with diabetes might significantly affect the estimate of insulin resistance by HOMA, as these drugs are known to decrease fasting plasma glucose without substantially changing fasting plasma insulin [16]. It seems, however, unlikely because Bonora et al [17] and Emoto et al [18] showed that in the validation studies of HOMA, the correlation of insulin sensitivity estimated by such method and that measured by a glucose clamp was not substantially different in diet-treated and sulfonylurea-treated type 2 diabetes mellitus. Furthermore, no significant difference was observed in some variables including BMI, leptin, adiponectin, and IL-6 between diet-treated and sulfonylurea-treated diabetic patients (data not shown). Therefore, we estimated HOMA-IR in diet-treated and sulfonylurea-treated diabetic patients.

2.1. Data analysis

Data were presented as means ± SEM. Statistical analysis was conducted using the StatView 5 system (Statview, Berkeley, CA). The means of 2 groups were compared with Student t test. Spearman rank correlation coefficient analysis was performed to calculate a correlation. $P < .05$ was considered significant.

3. Results

The subjects studied were all Japanese type 2 diabetic patients (75 men and 23 women) with an age range of 41 to 84 years (62.7 ± 0.9 years) and a BMI of 17.9 to 26.7 kg/m^2

Table 1
Clinical characteristics in insulin-resistant and insulin-sensitive diabetic patients

	Insulin-resistant	Insulin-sensitive	P
No. of subjects	36	62	
Age (y)	61.9 ± 1.7	63.2 ± 1.0	.249
Male/female	29/7	46/16	.239
HOMA-IR	3.72 ± 0.24	1.65 ± 0.06	<.001
Diabetes duration (y)	10.8 ± 1.5	11.3 ± 0.9	.379
Smoking (none/previous/current)	12/15/9	23/19/20	.245
Sulfonylureas/diet	30/6	54/8	.306
BMI (kg/m^2)	23.8 ± 0.3	22.6 ± 0.3	.003
Systolic blood pressure (mm Hg)	140 ± 3	135 ± 3	.129
Diastolic blood pressure (mm Hg)	87 ± 2	80 ± 1	.004
Fasting glucose (mg/dL)	153 ± 3	138 ± 3	.003
Fasting insulin (μU/mL)	10.0 ± 0.7	4.9 ± 0.2	<.001
HbA_{1c} (%)	7.3 ± 0.2	6.9 ± 0.1	.014
Triglycerides (mg/dL)	168 ± 16	108 ± 5	<.001
Total cholesterol (mg/dL)	213 ± 6	197 ± 4	.019
HDL-C (mg/dL)	54 ± 2	59 ± 2	.034
Leptin (ng/mL)	6.6 ± 0.8	4.8 ± 0.4	.015
Adiponectin (μg/mL)	10.9 ± 1.0	13.2 ± 0.7	.027
IL-6 (pg/mL)	1.8 ± 0.2	2.1 ± 0.3	.217

Table 2
Correlation of IL-6, leptin, and adiponectin to measures of variables in diabetic patients

	IL-6		Leptin		Adiponectin	
	r	*P*	*r*	*P*	*r*	*P*
HOMA-IR	0.016	.871	0.291	.004	−0.288	.005
BMI	0.090	.375	0.338	<.001	−0.308	.002
Systolic blood pressure	0.169	.116	0.241	.025	−0.077	.472
Diastolic blood pressure	−0.061	.570	0.116	.281	−0.269	.012
HbA_{1c}	0.018	.861	−0.062	.543	−0.053	.605
Triglycerides	0.028	.785	0.093	.362	−0.338	<.001
Total cholesterol	−0.153	.133	0.184	.071	0.010	.922
HDL-C	−0.295	.004	0.106	.300	0.300	.003
Leptin	0.062	.544			0.002	.841
Adiponectin	−0.020	.841	0.002	.841		

(23.1 ± 0.2 kg/m^2). They were all nonobese [19]. The fasting plasma glucose was 141 ± 2 mg/dL, and glycosylated hemoglobin (HbA_{1c}) was 7.0% ± 0.1%. Fasting insulin level was 6.7 ± 0.4 μU/mL. Serum triglycerides, total cholesterol, and HDL-C levels were 130 ± 7, 203 ± 4, and 57 ± 1 mg/dL, respectively. Serum IL-6, leptin, and adiponectin concentrations were 1.99 ± 0.21 pg/mL (range, 0.5-19.3 pg/mL), 5.5 ± 0.4 ng/mL (range, 1.4-22.8 ng/mL), and 13.2 ± 0.7 μg/mL (range, 1.5-24.9 μg/mL), respectively. There was a wide variation in insulin resistance calculated from HOMA-IR in our diabetic patients (range, 0.51-8.55, 2.41 ± 0.14). Of 98 patients, 36 (37%) had HOMA-IR greater than 2.5, indicating that they are insulin resistant [2,3].

Table 1 shows the clinical profile between insulin-resistant and insulin-sensitive type 2 diabetic patients. Compared with insulin-sensitive type 2 diabetic patients, insulin-resistant patients had significantly higher levels of BMI, diastolic blood pressure, fasting glucose, fasting insulin, HbA_{1c}, triglycerides, total cholesterol, and leptin, and lower concentrations of HDL-C and adiponectin. No significant difference was observed in age, sex, diabetes duration, smoking status, status of medication for diabetes, systolic blood pressure, and IL-6 levels between the 2 groups.

The correlation between fasting IL-6 concentration and the factors associated with insulin resistance (HOMA-IR, BMI, systolic blood pressure, diastolic blood pressure, HbA_{1c}, triglycerides, total cholesterol, HDL-C, leptin, adiponectin) was investigated next (Table 2). The peripheral level of IL-6 was not associated with these variables in our patients. In contrast, serum leptin was positively correlated to HOMA-IR, BMI, and systolic blood pressure. Serum adiponectin was negatively correlated to HOMA-IR, BMI, diastolic blood pressure, and triglycerides, and positively correlated to HDL-C in our patients.

4. Discussion

Type 2 diabetes mellitus is a syndrome characterized by insulin resistance and/or defective insulin secretion [1]. There seems to be an ethnic difference in insulin resistance in type 2 diabetes mellitus. Haffner et al [20] surveyed the prevalence of type 2 diabetes mellitus in white patients and found that 92% of type 2 diabetic patients were insulin resistant. Chaiken et al [21] reported that 60% of type 2 diabetic patients with BMI of less than 30 kg/m^2 were insulin resistant in African American populations. We recently demonstrated that 40% of type 2 diabetic patients are insulin resistant in nonobese Japanese type 2 diabetic patients, indicating that they are divided into 2 variants: one with insulin resistance and the other with normal insulin sensitivity [2,3]. This finding was reconfirmed in the present study.

Japanese type 2 diabetic patients are unique in that they do not always manifest obesity. We previously showed that the mean BMI in representative epidemiological studies of Japanese type 2 diabetic patients is 23 to 25 kg/m^2, which is lower than that in studies of other ethnic populations such as whites [22]. Thus, this fascinating feature of Japanese type 2 diabetic patients, that they are not always obese, but are composed of individuals who are both insulin sensitive and insulin resistant, enables us to estimate the factors responsible for insulin resistance in type 2 diabetic patients without confounding the effects of obesity.

There are some factors associated with insulin resistance in nonobese Japanese type 2 diabetic patients [2-5]. Whereas BMI and triglycerides are considered to be the most important factors responsible for the evolution of insulin resistance, regional abdominal adipose tissue distribution per se contributes to insulin resistance in nonobese Japanese type 2 diabetic patients [6]. In distinct from white populations [23] and African American populations [24], subcutaneous and visceral fat areas are independently associated with insulin resistance in nonobese Japanese type 2 diabetic patients [6]. Not only serum triglyceride but also serum leptin and adiponectin levels are shown to be associated with insulin resistance in our populations [2-5]. Serum triglyceride level is positively correlated to visceral fat area [6]. Serum leptin level is positively correlated to subcutaneous fat areas, whereas serum adiponectin level is negatively correlated to visceral fat areas [4,5]. Thus, the factors associated with insulin resistance in nonobese Japanese type 2 diabetic patients are hypothesized to be linked to adipose tissue–related insulin resistance.

Interleukin-6 is another factor that is associated with adipose tissue–related insulin resistance in man. Human adipose tissue is shown to secrete IL-6, and this secretion is correlated with BMI in white healthy subjects [7]. In the present study, we first demonstrated that fasting serum IL-6 level is not responsible for insulin resistance, at least not in nonobese Japanese type 2 diabetic patients. This is a surprising finding because it is a commonly held belief that IL-6 has a key role in the assessment of insulin resistance in obese and type 2 diabetic patients [9,10]. Bastard et al [9] showed that not only leptin but also IL-6 is associated with BMI and insulin resistance, and that IL-6 and leptin are interrelated in white obese type 2 diabetic patients. Haffner

et al [10] demonstrated that the serum levels of IL-6 are associated with BMI and insulin resistance in obese type 2 diabetic patients.

Thus, the reason why serum IL-6 is not associated with BMI and insulin resistance in nonobese well-controlled unique Japanese type 2 diabetic patients is currently unknown. The possible explanation is the different clinical characteristics studied. The Japanese type 2 diabetic patients in our study were unique in that they were nonobese and were well controlled in terms of BMI, fasting glucose, and HbA_{1c}. Mean levels of BMI, fasting glucose, and HbA_{1c} were 23.1 kg/m^2, 141 mg/dL, and 7.0%, respectively. In contrast, the linkage of IL-6 to insulin resistance is confirmed in healthy obese subjects (mean BMI, 31.8 kg/m^2) and obese type 2 diabetic patients (mean BMI, 36.6 kg/m^2; mean fasting glucose, 11.1 mmol/L; mean BMI, 30.1 kg/m^2; mean fasting glucose, 213.4 mg/dL; mean HbA_{1c}, 8.7%) [7,9,10]. Thus, the degree of overweight or of hyperglycemia per se might lead to the close relationship between serum IL-6 and insulin resistance in man. In this respect, the recent study by Kern et al [25], which showed that although plasma IL-6 concentration is associated with insulin resistance, its release is greater in obese subjects especially when BMI exceeds 30 kg/m^2, is very interesting. Body mass index in our patients ranged from 16.0 to 26.8 kg/m^2, that is, nonobese [14]. Thus, it may be hypothesized that insulin resistance evoked by IL-6 is the result of elevated adiposity rather than IL-6 exerting a negative effect on insulin action. This hypothesis is supported by the study of Vozarova et al [26], which showed that although IL-6 was positively correlated to insulin resistance and adiposity, the relationship between IL-6 and insulin resistance disappeared after adjustment for adiposity in healthy nondiabetic populations. Using the euglycemic clamp technique, Carey et al [27] very recently demonstrated that plasma IL-6 concentrations are strongly related to fat mass, but are not indicative of insulin resistance in humans. Haffner et al [28] showed that proliferator-activated receptor γ agonist (rosiglitazone) has a beneficial effect on insulin resistance, but has no effect on serum concentrations of IL-6 in patients with type 2 diabetes mellitus. Steensberg et al [29] have shown that recombinant human IL-6 infusion into healthy humans does not result in impaired glucose disposal.

It may be argued that pancreatic β-cell function per se might affect HOMA-IR in Japanese type 2 diabetic patients because these patients have mild impairments in pancreatic β-cell function [30]. For that reason, we used serum levels of leptin and adiponectin as another index of insulin resistance and found that serum IL-6 level was not associated with serum levels of leptin and adiponectin in the present study.

One might argue that exercise per se affects the level of serum IL-6 in this study because Lyngs et al [31] recently demonstrated that IL-6 secretion by adipose tissue was totally suppressed during exercise. It seems unlikely, however, because our patients did not perform heavy exercises for at least 1 week before the study. Alternatively, the racial difference or the different genetic variation within the IL-6 gene might explain the discrepant results. Polymorphisms of the IL-6 gene are shown to influence insulin sensitivity in man [32].

Irrespective of this, adipose tissue may not play a major role in the determination of circulating IL-6 in our nonobese well-controlled unique Japanese type 2 diabetic patients. It is well known that IL-6 production by adipose tissue could explain only 10% to 30% of the whole circulating IL-6 concentration in humans [7]. Alternatively, adipose tissue–secreted IL-6 might function locally at the level of the adipocyte in a paracrine or autocrine fashion in the diabetic patients in our study. In this respect, our very recent study, which shows that tumor necrosis factor α system activity is not responsible for the evolution of insulin resistance in nonobese Japanese type 2 diabetic patients, is intriguing [33].

In summary, we demonstrated for the first time that although the number of patients with type 2 diabetes mellitus is limited, the peripheral level of IL-6 does not appear to be a major explanation of the mechanisms underlying insulin resistance, at least in nonobese well-controlled Japanese type 2 diabetic patients. Further studies should be undertaken to clarify whether other nonobese diabetic population would exhibit similar results.

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