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Soluble E-selectin, leptin, triglycerides, and insulin resistance in nonobese Japanese type 2 diabetic patients

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Abstract

The aim of the present study was to investigate the relationships between insulin resistance and soluble E-selectin, body mass index (BMI), leptin, and serum lipid profile including triglycerides in nonobese Japanese type 2 diabetic patients.

A total of 97 nonobese Japanese type 2 diabetic patients aged 43 to 84 years were examined. The duration of diabetes was 11.2 ± 0.8 years. In conjunction with BMI and fasting concentrations of plasma glucose, serum lipids (triglycerides, total cholesterol, and high-density lipoprotein cholesterol) and serum insulin, soluble E-selectin, and leptin were also measured. The low-density lipoprotein (LDL) cholesterol level was calculated using the Friedewald formula. Insulin resistance was estimated by the homeostasis model assessment. The subjects were divided into 2 groups according to the value of insulin resistance estimated by the homeostasis model assessment. Values greater than 2.5 were indicative of the insulin-resistant state, and values less than 2.5 were indicative of the insulin-sensitive state.

The insulin-resistant group had significantly higher levels of E-selectin, leptin, triglycerides, total and LDL cholesterol, and diastolic blood pressure as compared with the insulin-sensitive group. There was, however, no significant difference in age, sex, diabetes duration, BMI, systolic blood pressure, HbA1c, and high-density lipoprotein cholesterol between the 2 groups. Univariate regression analysis showed that insulin resistance was positively correlated to E-selectin ($r = 0.305$, $P = .003$), BMI ($r = 0.283$, $P = .006$), leptin ($r = 0.296$, $P = .004$), HbA1c ($r = 0.241$, $P = .018$), serum triglycerides ($r = 0.385$, $P < .001$), serum total ($r = 0.240$, $P = .019$) and LDL cholesterol ($r = 0.254$, $P = .013$) levels, and systolic ($r = 0.247$, $P = .024$) and diastolic ($r = 0.305$, $P = .006$) blood pressure. Multiple regression analyses showed that insulin resistance was independently predicted by serum E-selectin ($F = 18.4$), serum leptin ($F = 14.0$) and serum triglycerides ($F = 20.0$) levels, which explained 45.0% of the variability of insulin resistance.

From these results, it can be concluded that in conjunction with serum triglycerides and serum leptin, serum E-selectin is another important independent factor associated with insulin resistance in nonobese Japanese type 2 diabetic patients.

1. Introduction

Type 2 diabetes is a heterogeneous syndrome characterized by insulin resistance and/or defective insulin secretion [1,2]. There seem to be ethnic differences in insulin resistance in type 2 diabetes. 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 [3,4].

The mechanisms underlying insulin resistance in nonobese Japanese type 2 diabetes are not fully understood. We recently demonstrated that insulin resistance in nonobese Japanese type 2 diabetic patients is mostly associated with triglycerides but not with body mass index (BMI) [5,6]. The reduction in triglycerides level by bezafibrate [7] or exercise [8] leads to an enhancement in insulin action without affecting BMI in nonobese Japanese type 2 diabetic patients. Abassi et al [9] are the first to show that plasma insulin concentration is more tightly linked to plasma leptin concentration than is the BMI in human beings. Thus, in conjunction with serum triglycerides, leptin is suggested to

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be another factor that is linked to insulin resistance in nonobese Japanese type 2 diabetic patients.

Furthermore, there are some literatures suggesting that insulin resistance is closely associated with the pathogenesis of atherosclerosis. The earliest morphological evidence of atherosclerosis is the attachment of monocytes to the cell surface of the endothelium. Monocytes attach at the cell surface of adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). In contrast to ICAM-1 and VCAM-1, E-selectin is expressed only on activated endothelium [10]. Thus, E-selectin is hypothesized to be one of the most important adhesion molecules for the evolution of atherosclerosis. Whereas serum E-selectin level is reported to be high in type 2 diabetic patients, the relationship between serum concentration of E-selectin and insulin resistance is very limited [11-13]. Furthermore, the relationship has not yet been fully investigated in nonobese Japanese type 2 diabetic patients without confounding the effects of serum triglycerides and serum leptin levels. In this respect, a major problem is that the degree of overweight or of hyperglycemia, insulin therapy, or the medications known to improve insulin resistance is shown to affect serum soluble E-selectin level. Thus, the aim of the present study is to investigate the relationship between insulin resistance andÂserum E-selectin in nonobese unique Japanese type 2 diabetic patients taking into account of the effects of leptin, triglycerides, BMI, and hemoglobin (Hb) A1c. This is the first description that in conjunction with serum triglycerides and serum leptin, serum E-selectin is another independent factor closely associated with insulin resistance in nonobese Japanese type 2 diabetic patients who had no insulin therapy and no evidence of diabetic vascular complications.

2. Subjects and methods

Ninety-seven Japanese type 2 diabetic patients who visited our clinic were enrolled for the present study. Type 2 diabetes mellitus was diagnosed based on the criteria of the World Health Organization [14]. The patients who had chronic heart or renal failure, symptomatic coronary heart disease, symptomatic stroke, and symptomatic peripheral artery disease were excluded. They had no evidence of current acute illness including clinically significant infectious disease. Their age and BMI levels were 62.9 ± 0.9 years (mean ± SEM) and 23.0 ± 0.2 (range, 19.1 to 26.7 kg/m^2), respectively. They all were nonobese [15]. The duration of diabetes was 11.2 ± 0.8 (range, 1 to 35 years). HbA1c level was 7.0% ± 0.1% (range, 5.2% to 10.4%). Systolic and diastolic blood pressure was 137 ± 2 and 83 ± 1 mm Hg, respectively. Forty-two of 97 patients had hypertension that was treated with angiotensin-converting enzyme inhibitors (21/42), calcium-channel blockers (20/42), or both (1/42). Eighty-three patients were taking sulfonylureas (gliclazide) and the rest with diet alone. Seventeen and 14 of 97 patients were treated with bezafibrate and 3-hydroxy-3 methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, respectively. They all were not treated with insulin, biguanides, or pioglitazone. All subjects had ingested at least 150 g of carbohydrate for the 3 days preceding the study. They did not consume alcohol or perform heavy exercise for at least 1 week before the study.

Blood was drawn at the morning after a 12-hour fast. Plasma glucose was measured with glucose oxidase method. The triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol 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 greater than 25 μU/mL and 7% for insulin less than 25 μU/mL, respectively. There was no detectable cross-reactivity of proinsulin in the insulin assay. Soluble E-selectin was measured by commercially available enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, Minn) using baseline samples. Serum leptin concentration was measured with a radioimmunoassay kit (Linco Research, St Charles, Mo) using specific human leptin antibody. The intra-assay and interassay CVs were less than 6% for E-selectin and leptin. Samples for insulin, E-selectin, and leptin were prepared, frozen, and stored at −70°C until the assay. The estimate of insulin resistance by homeostasis model assessment (HOMA-IR) was calculated with the formula: fasting serum insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5 [16]. The HOMA-IR value of normal glucose tolerant subjects was 1.6 ± 0.9 (mean ± SD), and we defined the value greater than 2.5 (mean ± SD of normal glucose-tolerant subjects) as an insulin-resistant state and the value less than 2.5 as an insulin-sensitive state [5,6]. The threshold value for insulin resistance in our study (ie, 2.5) is similar to that (2.77) reported in nonobese subjects with no metabolic disorders reported by Borona et al [17].

3. Statistical analysis

Data are presented as mean ± SEM. Statistical analyses were conducted using the StatView 5 system (StatView, Berkeley, Calif). Means of 2 groups were compared with Student t test. Simple (Spearman rank) correlation coefficients between HOMA-IR and measures of variables were calculated, and a stepwise multiple regression analysis was then used to evaluate the independent association of these variables with HOMA-IR. P value less than .05 was considered as significant. In multivariate analysis, F value ≥ 4 was considered significant.

4. Results

Table 1 illustrates the mean ± SEM of the clinical characteristics and clinical profile in insulin-resistant and insulin-sensitive nonobese Japanese type 2 diabetic patients. HOMA-IR values in the patients with insulin resistance and normal insulin sensitivity were 3.68 ± 0.25 and 1.63 ±

0.06, respectively. Thirty-two (30%) of 97 type 2 diabetic patients had HOMA-IR of greater than 2.5, indicating that they are insulin-resistant. There was no significant difference in age, duration of diabetes, BMI, HbA1c, and HDL cholesterol levels between the 2 subpopulations. Fasting glucose and insulin concentrations were significantly higher in insulin-resistant group than in insulin-sensitive group. In contrast, the patients with insulin resistance had significantly higher concentrations of E-selectin (58.2 ± 4.2 vs 47.2 ± 2.3 mg/dL, $P = .008$), leptin (6.18 ± 0.73 vs 4.47 ± 0.34 mg/dL, $P = .009$), triglycerides (148 ± 12 vs 109 ± 5 mg/dL, $P < .001$), total (213 ± 6 vs 196 ± 4 mg/dL, $P = .018$), and low-density lipoprotein (LDL) cholesterol (134 ± 6 vs 120 ± 4 mg/dL, $P = .018$) as compared with those with normal insulin sensitivity. Whereas no significant difference was observed in systolic blood pressure, diastolic blood pressure was significantly higher in insulin-resistant group than in insulin-sensitive group. There was no significant difference in the mode of therapy for hypertension or lipidemia between the 2 groups (data not shown).

Spearman rank correlations of insulin resistance with measures of variables were calculated for all our diabetic patients (Table 2). Insulin resistance was positively correlated with E-selectin, leptin, triglycerides, BMI, HbA1c, and total and LDL cholesterol levels. Other variables including age, sex, duration of diabetes, and HDL cholesterol were not associated with insulin resistance.

Multiple regression analyses were carried out using the stepwise procedure. The analysis included insulin resistance as a dependent variable and candidate risk factors (E-selectin, leptin, triglycerides, BMI, HbA1c, total cholesterol, and LDL cholesterol) as independent variables. Insulin resistance was independently predicted by serum concentrations of E-selectin, leptin, and triglycerides, which explained 45.0% of the variability of insulin resistance in our patients. Other variables including BMI, HbA1c, and total and LDL cholesterol were not independently associated with insulin resistance in our nonobese Japanese type 2 diabetic patients.

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

	Insulin-resistant	Insulin-sensitive	*P*
HOMA-IR	3.68 ± 0.25	1.63 ± 0.06	<.001
Number of subjects	32	65	
M/F	30/9	42/5	.384
Age (y)	62.4 ± 1.7	63.1 ± 1.0	.360
BMI (kg/m^2)	23.4 ± 0.3	22.8 ± 0.2	.064
Duration of diabetes (y)	11.3 ± 1.6	11.1 ± 0.8	.459
HbA1c (%)	7.2 ± 0.2	6.9 ± 0.1	.071
HDL cholesterol (mg/dL)	56 ± 2	60 ± 2	.135
Fasting glucose (mg/dL)	151 ± 4	137 ± 3	.005
Fasting insulin (μU/mL)	10.0 ± 0.7	4.8 ± 0.2	<.001
E-selectin (mg/dL)	58.2 ± 4.2	47.2 ± 2.3	.008
Leptin (mg/dL)	6.18 ± 0.73	4.47 ± 0.34	.009
Triglycerides (mg/dL)	148 ± 12	109 ± 5	<.001
Total cholesterol (mg/dL)	213 ± 6	196 ± 4	.018
LDL cholesterol (mg/dL)	134 ± 6	120 ± 4	.018
Systolic blood pressure (mm Hg)	141 ± 3	135 ± 2	.081
Diastolic blood pressure (mm Hg)	88±2	81±1	.001

Table 2
Correlation of insulin resistance to measures of variables in diabetic patients

	r	*P*
E-selectin	0.305	.003
Leptin	0.296	.004
Triglycerides	0.385	<.001
BMI	0.283	.006
HbA1c	0.241	.018
Total cholesterol	0.240	.019
LDL cholesterol	0.254	.013
Systolic blood pressure	0.247	.024
Diastolic blood pressure	0.305	.006
Age	−0.065	.522
Sex	0.007	.946
HDL cholesterol	−0.178	.804
Duration of diabetes	−0.018	.860

Finally, the relationships between soluble E-selectin and serum leptin, BMI, or serum triglycerides level were investigated. There were no significant relationships between serum soluble E-selectin level and serum leptin, BMI, or serum triglycerides level in our patients (data not shown).

5. Discussion

Type 2 diabetes is a heterogenous syndrome characterized by insulin resistance and/or defective insulin secretion [1,2]. There seems to be ethnic difference in insulin resistance in type 2 diabetes. Haffner et al [18] recently disclosed that 92% of type 2 diabetic patients are insulin-resistant in white populations. In contrast, Chaiken et al [19] previously showed that 60% of type 2 diabetic patients are insulin-resistant in black Americans with a BMI less than 30 kg/m^2. Using minimal model approach shown by Bergman et al [20], our team previously demonstrated that Japanese type 2 diabetic patients are divided into 2 variants: one with primary insulin resistance and the other with normal insulin sensitivity [3,4]. Thereafter, we have shown that 40% of type 2 diabetic patients are insulin-resistant in Japanese populations [5]. In conjunction with the present study that 30% of type 2 diabetic patients are insulin-resistant in nonobese Japanese type 2 diabetic patients, Japanese type 2 diabetic patients are assumed to be unique in terms of clinical profiles.

There are some factors associated with insulin resistance in nonobese Japanese type 2 diabetic patients. We recently demonstrated that serum triglycerides but not BMI are mostly associated with insulin resistance in nonobese Japanese type 2 diabetic patients [5,6]. Thereafter, our group clarified that not only serum leptin but also adiponectin levels are linked to insulin resistance in nonobese Japanese type 2 diabetic patients [21,22]. Serum triglyceride level is positively correlated to visceral fat areas in nonobese Japanese type 2 diabetic patients [23]. Serum

leptin level is positively correlated to subcutaneous fat areas, whereas serum adiponectin level is negatively correlated to visceral fat areas in nonobese Japanese type 2 diabetic patients [21,22]. 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.

Another factor that is associated with insulin resistance is adhesion molecules such as E-selectin, ICAM-1, and VCAM-1. These adhesion molecules are associated with the evolution of atherosclerosis. Atherosclerosis is assumed to be linked to insulin resistance in human beings. Thus, these adhesion molecules are suggested to be associated with insulin resistance in nonobese Japanese type 2 diabetic patients. In contrast to ICAM-1 and VCAM-1, E-selectin is expressed only on activated endothelium [10]. We therefore investigated the relationship between insulin resistance and serum soluble E-selectin in our nonobese unique Japanese type 2 diabetic patients.

In the present study, we disclosed that not only serum triglyceride but also serum soluble E-selectin and serum leptin levels are higher in insulin-resistant group than in insulin-sensitive groups in nonobese Japanese type 2 diabetic patients matched for sex. Furthermore, in conjunction with serum triglyceride and leptin, E-selectin is independently associated with insulin resistance in nonobese Japanese type 2 diabetic patients. It may be argued that our results are influenced by sex because leptin concentration is influenced by sex. However, not only insulin resistance but also serum triglycerides and E-selectin were not affected by sex in our present study.

Interestingly, serum leptin and triglycerides levels were independently associated with insulin resistance, whereas BMI was not, in our nonobese Japanese type 2 diabetic patients. Serum leptin level is shown to be associated with subcutaneous fat area in nonobese Japanese type 2 diabetic patients [21]. In contrast, serum triglyceride level is shown to be reflective of visceral abdominal fat area in nonobese Japanese type 2 diabetic patients [23]. Thus, body fat distribution but not the degree of BMI seems to affect insulin resistance in nonobese unique Japanese type 2 diabetic patients. This idea is supported from the recent study shown by Abassi et al [9] that plasma insulin concentration is more tightly linked to plasma leptin concentration than is the BMI. We recently demonstrated that both subcutaneous and visceral abdominal fat areas are independently associated with insulin resistance in nonobese Japanese type 2 diabetic patients [23].

E-selectin level was not associated with adipose tissue–related insulin resistance such as leptin, triglycerides, and BMI in our present study. Thus, E-selectin is considered to be another most important factor associated with insulin resistance in nonobese Japanese type 2 diabetic patients.

The mechanisms underlying the relationship between insulin resistance and soluble E-selectin are not known at present. One possible explanation for the relationship is nitric oxide released from endothelium. Steinberg et al [24] showed that insulin resistance is associated with blunted endothelium-dependent vasodilation and that this phenomenon is related to low nitric oxide release from endothelium. Elevated E-selectin level is known to be reflective of endothelial damage [25]. Another possible explanation for the finding is the mode of therapy. Intensive insulin therapy is reported to reduce serum E-selectin level in diabetic patients [26]. Agents that improve insulin resistance are shown to reduce serum E-selectin concentration. Cominacini et al [27] reported that troglitazone decreased serum E-selectin level in patients with type 2 diabetes. In the present study, our patients were not treated with insulin therapy or the medications known to improve insulin resistance such as biguanide or pioglitazone. Finally, the role of oxidative stress should not be overlooked in type 2 diabetic patients. Cominacini et al [11] showed that serum E-selectin concentration is related to plasma hydroperoxides and to susceptibility to LDL to oxidation in type 2 diabetic patients.

Irrespective of this, it can be concluded that in conjunction with serum triglycerides, serum E-selectin and leptin are another independent factors associated with insulin resistance in nonobese unique Japanese type 2 diabetic patients.

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