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Correlation between the adiponectin-leptin ratio and parameters of insulin resistance in patients with type 2 diabetes

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Abstract

We studied the correlation between the adiponectin-leptin (A/L) ratio and parameters of insulin resistance in 220 Japanese patients with type 2 diabetes (138 men and 82 women). Body mass index (BMI), triglycerides (TGs), HDL cholesterol (HDL), and preheparin serum lipoprotein lipase (LPL mass) were examined as laboratory parameters of the insulin resistance. The correlations between these laboratory parameters and adiponectin, leptin, or A/L ratio were studied. Adiponectin levels correlated significantly with BMI ($r = -0.298$, $P = .0003$), TGs ($r = -0.221$, $P = .0092$), HDL ($r = 0.31$, $P = .0002$), and LPL mass ($r = 0.26$, $P = .0021$) in men, and with TGs ($r = -0.29$, $P = .0093$), HDL ($r = 0.239$, $P = .0338$), and LPL mass ($r = 0.499$, $P < .0001$) in women. Leptin levels correlated significantly with only BMI ($r = 0.31$, $P = .0002$) in men, and with BMI ($r = 0.71$, $P < .0001$) and TGs ($r = 0.26$, $P = .0201$) in women. Adiponectin and leptin levels tended to correlate with these parameters in an opposite manner. On the other hand, A/L ratio significantly correlated with BMI ($r = -0.4$, $P < .0001$), TG ($r = -0.199$, $P = .0192$), HDL ($r = 0.235$, $P = .0054$), and LPL mass ($r = 0.244$, $P = .0390$) in men, and with BMI ($r = -0.482$, $P < .0001$), TG ($r = -0.402$, $P = .0002$), HDL ($r = 0.358$, $P = .0011$), and LPL mass ($r = 0.487$, $P < .0001$) in women. Next, the patients were divided into 3 groups classified by their fasting plasma glucose (FPG) level, and the correlations between the parameters and A/L ratio or homeostasis model assessment (HOMA-R), and the correlation between A/L ratio and HOMA-R were investigated in each group. Significant correlations between the parameters and A/L ratio were tended to be observed as the FPG level rose; however, the significant correlations between the parameters and HOMA-R were no longer seen as FPG level elevated. The results suggested that the A/L ratio was effective in relevance as a parameter of insulin resistance to adiponectin or leptin alone, and a more sensitive and reliable marker of insulin resistance than HOMA-R as the FPG level elevated, in patients with type 2 diabetes.

1. Introduction

In our modern society, changes in lifestyle, such as consumption of calorie-rich foods and lack of exercise, lead to excessive accumulation of body fat, resulting in obesity, which triggers lifestyle-related diseases such as diabetes, hyperlipidemia, and atherosclerosis [1,2].

Molecular-biological approaches to the study of the mechanism by which accumulation of body fat triggers various pathological conditions are not always satisfactory. However, genes that are specifically expressed in adipose tissue have been identified by large-scale random sequence analysis of genes expressed in adipose tissue [3] and have been mapped. This mapping revealed that an unexpectedly large number of genes of functional proteins were expressed in adipose cells, and that most of such proteins were secretory proteins. In addition, adipose cells were found not only to function as energy storage organs but also to secrete cytokines [1,2]. From 1995 to 1996, proteins that are specifically expressed and secreted by adipose cells were identified and named Acrp30 [4], AdipoQ [5], apM1 [3], and GBP28 [6]. A study of the amino acid sequences of these proteins revealed that the proteins were identical to each other and were named adiponectin. The level of this protein, adiponectin, has been reported to decrease as the body mass index (BMI) increases and to correlate negatively with insulin resistance [7-10]. Likewise, leptin is a protein whose genes are specifically expressed in adipose cells. In obese people, expressions of leptin in adipose cells

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and leptin concentration in blood are significantly high, and leptin can correspondingly be used as a sensitive chemical marker for the diagnosis of obesity and obesity-related diseases [11-13]. The effects of adiponectin and leptin on energy metabolism differ; adiponectin affects the peripheral regulation, whereas leptin affects the central regulation. The ratio of leptin to adiponectin has been recently proposed as a potential index for comprehensively identifying obesity in cynomolgus monkeys [14]. Obesity is commonly associated with insulin resistance and is a major risk factor for the development of type 2 diabetes. Moreover, the ratio of adiponectin to leptin has been reported to predict insulin sensitivity and potential cardiovascular risk in HIV-infected patients [15].

In this study, we scrutinized adiponectin, a secretory protein that is negatively correlated with BMI despite the fact that it is specifically expressed in adipose cells that play an important role in development of insulin resistance, and leptin, the level of which correlates positively with the BMI. Because insulin resistance has recently attracted attention as a factor that may relate BMI, hypertriglyceridemia, hypo HDL cholesterol (HDL), and a decreased level of lipoprotein lipase (LPL) [16-19], we investigated the correlation between the adiponectin-leptin (A/L) ratio and the parameters of insulin resistance in patients with type 2 diabetes by scrutinizing how the A/L ratio is related to BMI, triglycerides (TGs), HDL, and preheparin serum LPL mass. Next, because homeostasis model assessment (HOMA-R) does not allow an accurate decision affected by the results caused by a decreased secretion of insulin due to glucotoxicity [20,21], we studied the relationships between these laboratory parameters of the insulin resistance and the A/L ratio or HOMA-R by fasting plasma glucose (FPG) level, and the relationship between the A/L ratio and the HOMA-R [22,23] by FPG level to examine the usefulness of A/L ratio for assessing insulin resistance in type 2 diabetes.

2. Research design and methods

2.1. Subjects

The subjects with type 2 diabetic patients were selected randomly from our outpatient clinic of Showa University Fujigaoka Hospital in August 2002. After excluding patients who had received insulin treatment or a class of insulin-sensitizing agents previously, and/or had a serum creatinine level of 1.2 mg/dL or above, 220 patients (138 men and 82 women) who gave informed consent for blood collection were enrolled in the study. Table 1 shows the background factors of the male and female subjects, and background factors with patients classified into 3 groups according to their FPG level. The FPG level was the only factor differentiating these 3 groups. Other considerable factors such as age, period from onset of diabetes, BMI, adiponectin, and leptin values were more or less the same.

2.2. Study design

The subjects were divided by their sex, and the relationships between each of the parameters (BMI, TGs, HDL, and LPL mass) and adiponectin, leptin, or A/L ratio were examined. Next, the subjects were divided into 3 groups by their FPG level (below 140 mg/dL, group A; between 140 and 169 mg/dL, group B; and 170 mg/dL or

Table 1
Clinical characteristics of the study population

Sex	Male				Female			
	All (N = 138)	Group A (N = 76)	Group B (N = 36)	Group C (N = 26)	All (N = 82)	Group A (N = 49)	Group B (N = 17)	Group B (N = 16)
Age (y)	57.7 ± 10.7	57.0 ± 11.8	59.6 ± 8.5	57.3 ± 10.0	59.3 ± 9.8	60.6 ± 9.5	59.2 ± 11.5	55.8 ± 8.0
Duration (y)	9.4 ± 7.8	8.6 ± 7.6	9.5 ± 7.0	11.3 ± 9.4	9.2 ± 6.1	8.7 ± 5.9	8.3 ± 6.1	11.0 ± 6.7
BMI (kg/m^2)	23.8 ± 2.7	24.0 ± 3.0	23.9 ± 1.9	23.0 ± 2.4	24.7 ± 4.1	24.5 ± 4.3	26.0 ± 3.5	23.8 ± 4.4
FPG (mg/dL)	141.6 ± 44.2*	115.0 ± 15.8^{a,b}	150.6 ± 7.4^{b,c}	206.8 ± 56.5^{a,c}	142.5 ± 34.8*	120.3 ± 13.6^{a,b}	153.8 ± 10.1^{b,c}	198.6 ± 23.3^{a,c}
FIRI (μU/mL)	7.8 ± 5.6	7.2 ± 5.1	7.5 ± 4.4	9.9 ± 8.1	8.3 ± 6.2	7.9 ± 6.1	10.2 ± 7.7	7.8 ± 4.4
HDL (mg/dL)	48.0 ± 11.8*	45.6 ± 12.7^{a,b}	50.8 ± 10.3^{c}	51.2 ± 9.7^{c}	52.8 ± 14.5*	53.3 ± 15.6	49.4 ± 14.8	54.7 ± 9.8
TG (mg/dL)	117.5 ± 56.4	115.1 ± 59.7	123.0 ± 55.3	116.9 ± 48.8	121.8 ± 67.2	110.0 ± 56.4	166.5 ± 104.7	129.3 ± 74.3
HbA1c (%)	7.5 ± 1.6*	7.4 ± 1.8	7.6 ± 1.3	7.6 ± 1.1	8.0 ± 1.7*	7.4 ± 1.6^{a,b}	8.4 ± 1.7^{c}	8.7 ± 1.6^{c}
Adiponectin (μg/mL)	5.6 ± 3.2*	5.4 ± 3.5	5.5 ± 2.5	6.4 ± 3.1	8.3 ± 4.3*	8.9 ± 4.4	7.1 ± 3.7	7.8 ± 4.0
Leptin (ng/mL)	3.8 ± 1.8*	3.6 ± 1.8	4.0 ± 1.6	4.0 ± 1.7	9.1 ± 5.5*	8.9 ± 5.4	9.8 ± 4.9	8.6 ± 6.5
LPL mass (ng/mL)	37.0 ± 12.6*	36.4 ± 13.0	37.6 ± 11.7	38.2 ± 13.0	47.5 ± 17.0*	50.3 ± 17.1	41.9 ± 18.4	42.6 ± 21.1
HOMA-R	2.8 ± 2.6	2.1 ± 1.5^{a,b}	2.7 ± 1.7^{b,c}	5.2 ± 4.6^{b,c}	2.9 ± 2.3	2.3 ± 1.8	4.0 ± 3.2	3.7 ± 2.1

Data are the means ± SD.

Comparison was made by Wilcoxon signed rank test by sex and in each group by their sex.

[a] $P < .05$, compared to group B.

[b] $P < .05$, compared to group C.

[c] $P < .05$, compared to group A.

* $P < .05$, all in men vs all in women.

above, group C), taking into account the influence of the decrease in insulin secretion due to glucotoxicity resulting from chronic hyperglycemia. In these 3 groups, the correlations between the A/L ratio or HOMA-R and the various parameters (BMI, TG, HDL, and LPL mass) were examined.

2.3. Measurement

After a 10- to 12-hour overnight fast, a fasting blood sample was obtained to determine FPG, fasting plasma insulin level (FIRI), and the other parameters. Serum levels of TGs, HDL, and creatinine were measured by enzymatic methods using an autoanalyzer (HITACHI 7350 Analyzer, Tokyo, Japan). Serum leptin concentrations were measured by a commercially available radioimmunoassay kit (human leptin RIA kit; Cosmic Corporation, Tokyo, Japan). Serum adiponectin concentration was determined by enzyme-linked immunosorbent assay (ELISA) (adiponectin ELISA kit; Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan) [7]. The plasma fasting glucose level was measured by an automated enzymatic method. Lipoprotein lipase mass in preheparin serum was measured by sandwich ELISA, as described previously [19]. For the assay, a kit from Daiichi Pure Chemicals, Tokyo, was used. Serum insulin was measured using an immunoradiometric assay Kit (Insulin Riabead II Kit; Abbott, Japan). The insulin resistance index assessed by the homeostasis model assessment was calculated as follows [22,23]: HOMA-R = FIRI (μU/mL) × FPG (mg/dL)/405. The HbA1c was measured by high-performance liquid chromatography.

2.4. Statistical analyses

All statistical analyses were performed with the Statview 4.5 system (Abacus Concepts, Berkeley, Calif) for Apple computer. The Wilcoxon signed rank test was used where appropriate for comparisons of clinical parameters between men and women and was performed in each subgroup by sex. Relationships were analyzed by simple correlation. All values are the mean ± SD, and a value of $P < .05$ was considered statistically significant.

3. Results

3.1. Simple linear regression analyses between adiponectin, leptin, or A/L ratio and various parameters (BMI, TG, HDL, and LPL mass)

Adiponectin levels correlated significantly with BMI, TGs, HDL, and LPL mass in men, and with TGs, HDL, and LPL mass in women. Leptin levels correlated significantly with only BMI in men and with BMI and TGs in women. Adiponectin and leptin levels tended to correlate with these parameters in an opposite manner. On the other hand, A/L ratio significantly correlated with all parameters in both men and women (Table 2).

3.2. Simple linear regression analyses between the A/L ratio or HOMA-R and BMI, TGs, LPL mass, and HDL, as well as between A/L ratio and HOMA-R in patients distributed by their FPG level

Significant correlations between A/L ratio and BMI were found for men in group A ($r = -0.337$, $P = .0007$), group B ($r = -0.581$, $P = .0001$), and group C ($r = -0.462$, $P = .0165$), and for women in group A ($r = -0.482$, $P = .0004$), group B ($r = -0.571$, $P = .0194$), and group C ($r = -0.547$, $P = .0267$). On the other hand, no significant correlations were found between HOMA-R and BMI in the groups of men; significant correlations were found for women in group A ($r = 0.694$, $P < .0001$) and group B ($r = 0.628$, $P = .0079$). Significant correlations between A/L ratio and TGs were found only for men in group A ($r = -0.242$, $P = .0349$) and for women in group A ($r = -0.442$, $P = .0013$) and group C ($r = -0.536$, $P = .0308$); however, no significant correlations were observed between HOMA-R and TGs in any of the men and only in group A ($r = 0.414$, $P = .0031$) for the women. Significant correlations between A/L ratio and LPL mass were found only for men in group A ($r = 0.350$, $P = .0019$) and for women in group A ($r = 0.472$, $P = .007$) and group C ($r = 0.508$, $P = .0437$), whereas no significant correlations between HOMA-R and LPL mass were observed in any group for either men or women. Significant correlations between A/L ratio and HDL were

Table 2
The result of correlation between adiponectin, leptin, or A/L ratio and BMI, TG, HDL, and LPL mass of the patients

	Sex	Adiponectin		Leptin		A/L ratio	
		r	*P*	*r*	*P*	*r*	*P*
BMI	Male	−0.298	.0003*	0.310	.0002*	−0.400	<.0001*
	Female	−0.152	.1858	0.704	<.0001*	−0.482	<.0001*
TG	Male	−0.221	.0092*	0.011	.8968	−0.199	.0192*
	Female	−0.290	.0093*	0.26	.0201*	−0.402	.0002*
HDL	Male	0.310	.0002*	−0.052	.5463	0.235	.0054*
	Female	0.239	.0338*	−0.166	.1441	0.358	.0011*
LPL mass	Male	0.260	.0021*	−0.018	.8376	0.244	.0390*
	Female	0.499	<.0001*	−0.137	.2342	0.487	<.0001*

Comparison was made by simple linear regression analyses.
* Statistically significant at $P < .05$.

Table 3
Correlations between A/L ratio or HOMA-R and BMI, TG, LPL mass, and HDL of the subjects in each group, as well as between A/L ratio and HOMA-R in each group

Male	A/L ratio			HOMA-R		
	Group A (N = 76)	Group B (N = 36)	Group C (N = 26)	Group A (N = 76)	Group B (N = 36)	Group C (N = 26)
BMI	$r = -0.337$	$r = -0.581$	$r = -0.462$	$r = -0.009$	$r = 0.285$	$r = 0.230$
	$P = .0007$*	$P = .0001$*	$P = .0165$*	$P = .9411$	$P = .0924$	$P = .2728$
TG	$r = -0.242$	$r = -0.188$	$r = -0.006$	$r = 0.010$	$r = 0.076$	$r = -0.134$
	$P = .0349$*	$P = .2736$	$P = .9760$	$P = .9288$	$P = .6626$	$P = .5272$
LPL	$r = 0.350$	$r = 0.184$	$r = -0.062$	$r = -0.033$	$r = 0.182$	$r = 0.040$
	$P = .0019$*	$P = .2854$	$P = .7653$	$P = .777$	$P = .2908$	$P = .8515$
HDL	$r = 0.277$	$r = 0.144$	$r = 0.291$	$r = -0.157$	$r = -0.08$	$r = -0.380$
	$P = .0152$*	$P = .4034$	$P = .1509$	$P = .1772$	$P = .6456$	$P = .0608$
A/L ratio				$r = -0.320$	$r = -0.422$	$r = -0.181$
				$P = .0046$*	$P = .0097$*	$P = .3919$
Female	**A/L ratio**			**HOMA-R**		
	Group A (N = 49)	Group B (N = 17)	Group C (N = 16)	Group A (N = 49)	Group B (N = 17)	Group C (N = 16)
BMI	$r = -0.482$	$r = -0.571$	$r = -0.547$	$r = 0.694$	$r = 0.628$	$r = 0.24$
	$P = .0004$*	$P = .0194$*	$P = .0267$*	$P < .0001$*	$P = .0079$*	$P = .3781$
TG	$r = -0.442$	$r = -0.210$	$r = -0.536$	$r = 0.414$	$r = 0.365$	$r = 0.185$
	$P = .0013$*	$P = .4245$	$P = .0308$*	$P = .0031$*	$P = .152$	$P = .500$
LPL	$r = 0.472$	$r = 0.364$	$r = 0.508$	$r = -0.254$	$r = -0.238$	$r = -0.042$
	$P = .007$*	$P = .1533$	$P = .0437$*	$P = .0886$	$P = .3648$	$P = .8788$
HDL	$r = 0.327$	$r = 0.508$	$r = 0.231$	$r = -0.229$	$r = -0.109$	$r = -0.011$
	$P = .049$*	$P = .0362$*	$P = .3953$	$P = .1185$	$P = .6832$	$P = .9680$
A/L ratio				$r = -0.529$	$r = -0.568$	$r = -0.322$
				$P < .0001$*	$P = .0159$*	$P = .2283$

Comparison was made by simple linear regression analyses.
* Statistically significant at $P < .05$.

found only for men in group A ($r = 0.277$, $P = .015$) and for women in group A ($r = 0.327$, $P = .049$) and group B ($r = 0.508$, $P = .0362$), whereas no significant correlations between HOMA-R and HDL were observed in any group for either men or women (Table 3).

A/L ratio and HOMA-R correlated significantly both in men and women ($r = -0.209$, $P = .0139$ in men, $r = -0.48$, $P < .0001$ in women) (data not shown). When A/L ratio and HOMA-R were studied in patients distributed by their FPG level, significant correlations were observed in group A ($r = -0.320$, $P = .0046$ in men, $r = -0.529$, $P < .0001$ in women) and group B ($r = -0.422$, $P = .0097$ in men, $r = -0.568$, $P = .0159$ in women), but not in either men or women of group C.

4. Conclusions

For treatment of diabetic patients, it is important to measure insulin resistance because it plays a role in the development of atherosclerosis and diabetes. In the clinical setting, we frequently encounter patients who have already developed diabetes mellitus with increased FPG. Evaluating insulin resistance in these patients may be important in selecting drugs because of appearance of insulin-sensitizing agents in the market. Although the hyperinsulinemic euglycemic clamp [24,25] and steady-state plasma glucose [26] methods are the golden standard for estimating insulin resistance, they involve complicated procedures. The HOMA-R is a convenient means to evaluate insulin resistance [22,23], although some limitations have been reported, restricting its clinical use [20,21]. Indeed, several investigators report that HOMA-R and insulin action do not correlate highly or significantly, particularly in individuals with impaired glucose tolerance [27] and elderly patients with poorly controlled type 2 diabetes mellitus [28]. Ono et al [21] reported that HOMA-R is a useful index for determining insulin resistance at the FPG range of 80-170 mg/dL in patients with obese type 2 diabetes mellitus. In this study, we investigated the relationships between A/L ratio and HOMA-R in the subjects distributed by their sex and FPG level.

In recent years, as the molecular mechanism of adipose cells is elucidated, it is becoming clear that a large amount of proteins are secreted by adipose cells and how the proteins function. Adipose tissue secretes a variety of proteins: adiponectin, whose secretion is decreased by insulin resistance, and leptin, which increases as BMI increases. The effects of adiponectin and leptin on energy metabolism differ; adiponectin is thought to increase insulin sensitivity and tissue fat oxidation resulting in reduced circulating fatty acid levels and reduced liver and intramyocellular TG content [29,30], and leptin is thought to provide information

about nutritional status and fat mass to neural centers regulating feeding behavior, appetite, and energy expenditure [31]. The level of adiponectin decreases and the level of leptin increases with insulin resistance [32,33]. Moreover, adiponectin and leptin levels tend to correlate with the various parameters (BMI, TG, HDL, and LPL mass) in an opposite manner. Although the mechanisms and processes of these hormones remain unclear, they supposedly are involved in regulation of energy metabolism and manifestation of insulin resistance.

Yamauchi et al [34] created a condition in which adipose cells became atrophied as a result of HX531 administrations, so that proteins secreted by adipose cells would be removed. Under this condition, insulin resistance increased, and the increased insulin resistance improved when adiponectin was administered. Moreover, insulin resistance further improved when a physiological concentration of leptin was administered. Very recently, it was reported that the ratio of leptin to adiponectin was a potential index for comprehensively identifying obesity in cynomolgus monkeys [14]. Moreover, the A/L ratio was reported to predict insulin sensitivity and the potential cardiovascular risk in HIV-infected patients [15]. Therefore, we divided the subjects by their sex, and the relationships between each of the laboratory parameters of insulin resistance (BMI, TGs, HDL, and LPL mass) and adiponectin, leptin, or A/L ratio were studied. Out of the parameters studied, all but BMI in the groups of females exhibited a significant correlation with adiponectin alone, and BMI in the groups of males and females as well as TGs in the groups of females exhibited a significant correlation with leptin alone. On the other hand, all the parameters examined exhibited a significant correlation with A/L ratio. It thus appeared that the A/L ratio was a better marker of measurement for assessing insulin resistance than adiponectin or leptin alone.

Next, we examined the relationships between the laboratory parameters of insulin resistance and the A/L ratio or HOMA-R by FPG level, and the relationship between the A/L ratio and HOMA-R by FPG level to consider the influence of blood glucose concentration on A/L ratio or HOMA-R, because surrogate indexes on the basis of baseline values of insulin and glucose, such as the HOMA-R, have been reported to be accurate in case of mild type 2 diabetic patients treated by diet or low dose of diabetic drugs [35]. In this study, although there were no significant differences in BMI, period from onset of diabetes, age, adiponectin, and leptin concentration among the 3 groups of males and females, some of these parameters significantly correlated with the A/L ratio and/or HOMA-R in both the groups of males and females divided by their FPG level. In group A, these parameters correlated with the A/L ratio fairly well, whereas these parameters correlated with HOMA-R weakly. On the other hand, in groups B and C, the A/L ratio still correlated with some of these parameters; HOMA-R no longer correlated with either of the groups except BMI in females.

Disregarding the problem that HOMA-R might not be sensitive to monitor cases with lowered insulin secretion or insulin resistance resulting from glucotoxicity, we investigated the relationships between the A/L ratio and HOMA-R in the subjects distributed by their sex and FPG level. Significant correlations were found in both males and females with FPG levels below 170 mg/dL, but no correlations were found in those with FPG levels of 170 mg/dL or above. These results suggested that HOMA-R could not exactly be evaluated with insulin resistance at FPG levels above 170 mg/dL. It is assumed that the difference by FPG was made on the ground that glucotoxicity reduced endogenous insulin secretion making it impossible to accurately assess insulin resistance with HOMA-R. This assumption is backed up by the study on the relationships between each of the parameters of insulin resistance and the A/L ratio or HOMA-R in groups divided by FPG levels and the study on the relationship between the A/L ratio and HOMA-R in groups divided by their sex and FPG levels.

The results of the present study suggested that HOMA-R might not be useful for accurately assessing insulin resistance with FPG levels of 170 mg/dL or above, and that the A/L ratio might be a better marker of measurement for assessing of insulin resistance than HOMA-R and adiponectin or leptin alone. In this study, we did not investigate the correlation between the A/L ratio and *M* value, which was evaluated by the hyperinsulinemic euglycemic clamp technique using an artificial pancreas. In the future, it will be necessary to study the correlation between the A/L ratio and *M* value in type 2 diabetic patients to determine whether it is possible to use the A/L ratio as a marker for insulin resistance.

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