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ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 153–159
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Key role of insulin resistance in vascular injury among hemodialysis patients

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Received 6 February 2006; accepted 23 August 2006

Abstract

Insulin resistance prevails not only among diabetic patients but also among hypertensive and obese patients. The relationship between insulin resistance and cardiovascular diseases was investigated in hemodialysis (HD) patients. Eighty-one maintenance HD patients were enrolled. The homeostasis model assessment of insulin resistance (HOMA-IR) method was used to assess insulin resistance. The relationship of HOMA-IR with cardiovascular and all-cause events was assessed. Compared with nondiabetic patients (n = 55), diabetic patients (n = 26) showed higher HOMA-IR (2.5 ± 0.3 vs 1.4 ± 0.2, $P < .05$), lower ankle-brachial pressure index (ABI, 0.85 ± 0.09 vs 1.12 ± 0.02, $P < .01$), and shorter HD duration (3 ± 1 vs 9 ± 1 years, $P < .01$), although their body mass index was similar (22.3 ± 0.5 vs 21.5 ± 0.4 kg/m^2). Nondiabetic patients taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (n = 36) had lower HOMA-IR (1.2 ± 0.2 vs 1.8 ± 0.4, $P < .05$) and higher ABI (1.18 ± 0.02 vs 1.02 ± 0.05, $P < .01$) than those without (n = 17). Cardiovascular events were less common in HD patients with normal HOMA-IR ($P < .05$) or ABI ($P < .01$). Our data indicate that 69% of diabetic and 27% of nondiabetic patients have HOMA-IR greater than 1.6, implying reduced insulin sensitivity in HD patients. The present results provide evidence that angiotensin inhibition improves insulin resistance, possibly preventing vascular injury in HD patients. Finally, our findings suggest that insulin resistance is prognostic of cardiovascular events in HD patients.

1. Introduction

Cardiovascular disease is a frequent complication in hemodialysis (HD) patients, constituting a major cause of death in this population [1]. The prevention of arteriosclerotic disease is important among HD patients because it may not only improve the life expectancy of the patients but also decrease the total medical cost required for patients with end-stage renal disease. In addition to classic cardiovascular risk factors (hypertension, dyslipidemia, and hyperglycemia), HD patients are commonly exposed to additional risk factors related to uremia, including hyperhomocysteinemia, hyperparathyroidism, hyperphosphatemia, and calcium overload [1-5].

Insulin resistance is associated with multiple risk factors for atherosclerosis, and linked to atherosclerotic cardiovascular diseases in the general population [6]. Insulin resistance prevails in obese people and is also seen among the nonobese population. Insulin sensitivity is impaired in the young, lean, normotensive offspring of essential hypertensive subjects [7]. Recent advances in research on adipokines provide clues to understanding how obesity induces insulin resistance [8,9]. Although an obesity-related decrease in adiponectin was observed in HD patients, plasma adiponectin is very high in this population [8]. However, the mechanisms mediating insulin resistance among nonobese persons remain unclear. Chronic kidney disease can be divided into 5 stages [10]. We have previously shown that patients with chronic glomerulonephritis with mild renal insufficiency possess insulin resistance [11]. Insulin resistance may relate to pathophysiology common for all stages of chronic kidney diseases such as oxidative stress. Thus, insulin resistance may also associate with the pathogenesis of cardiovascular diseases in HD patients.

Parts of the data in this manuscript were presented at the 50th annual meeting of the Japanese Society of Dialysis Therapy and have been published in an abstract form [J Jap Soc Dial Ther 2005;38(Suppl 1):865].

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doi:10.1016/j.metabol.2006.08.010

Table 1
Case distribution of ABI and HOMA-IR (number of patients with type 2 diabetes mellitus)

	ABI <0.9	0.9 < ABI < 1.3	ABI > 1.3
HOMA-IR <1.6	9 (3)	35 (5)	4 (0)
1.6 < HOMA-IR < 2.5	2 (2)	13 (4)	0 (0)
HOMA-IR >2.5	4 (3)	12 (8)	2 (1)

Recent studies on patients with chronic kidney diseases with mild to moderate renal dysfunction have indicated that angiotensin inhibition not only slows the progression of renal disease to end-stage renal failure, but also decreases cardiovascular morbidity [12,13]. Furthermore, our recent results suggest that in addition to antioxidants, angiotensin inhibition was required to arrest progressive increase in pulse wave velocity in HD patients [3]. Fast pulse wave velocity indicates shorter cardiovascular survival in HD patients, and an attenuation of pulse wave velocity leads to an improvement in their survival. Although angiotensin could interact with insulin signaling in various pathways [14], the influence of angiotensin inhibition on insulin resistance in HD patients, as evaluated using the homeostasis model assessment of insulin resistance (HOMA-IR) method, remains obscure.

In the present study, we measured ankle-brachial pressure index (ABI) and HOMA-IR in HD patients. The prevalence of peripheral artery disease is high in this patient population [15]. Thus, ABI was used to assess vascular injury. We also measured free carnitine (FC), oxidized low-density lipoprotein (ox-LDL), and lipoprotein lipase (LPL) levels to examine their relationship to HOMA-IR and ABI [2,16,17]. In addition, we assessed whether HOMA-IR could predict cardiovascular events in HD patients.

2. Methods

Eighty-one patients undergoing maintenance HD (4 hours per session, 3 days/wk) in our clinics entered into the study and gave informed consent according to the Declaration of Helsinki [4]. HD was performed with standard bicarbonate dialysate (in millimoles per liter: Na, 140; K, 2; Cl, 110; HCO_3, 30; Ca, 1.5; Mg, 0.5) by using a high-flux hemodialyzer of either cellulose or synthetic membrane (surface area, 0.8-2.1 m^2) and heparin (2000-6000 U per session) as an anticoagulant. There were 26 (7 men and 19 women) patients with type 2 diabetes mellitus. Complete physical examinations were performed and medical histories were taken. Dry weight was carefully determined in each case to achieve a normotensive, edema-free state by using cardiothoracic ratio, plasma concentration of atrial natriuretic peptide, and inferior vena cava diameter, as detailed previously [3]. Before starting dialysis, blood was drawn to measure fasting plasma glucose (FPG), fasting plasma immunoreactive insulin (FPI), FC, and ox-LDL levels [2,18]. Blood pressure was assessed before dialysis with the patients in the supine position. HOMA-IR was calculated with the formula HOMA-IR = FPG (mg/dL) × FPI (microunits per milliliter)/405 [19]. A previous study using glucose clamp demonstrated that HOMA-IR was a reliable index of insulin resistance for patients with renal failure [20]. To evaluate vascular injury, ABI was determined [2]. On the day of the study, heparin (30 U/kg) was administered intravenously. Fifteen minutes later, a blood sample was taken to measure LPL [21].

Among 26 diabetic patients, 12 were on insulin treatment (8-32 U/d) and 5 were on nateglinide (180-360 mg/d). For these patients, blood samples were drawn to measure FPI and FPG before morning injection of insulin or morning oral hypoglycemic agents [22]. The other 9 diabetic patients were controlled by diet therapy alone. Doses of medication were adjusted to attain a glycosylated hemoglobin level of less than 6% [19]. No sulfonylurea agents were used because they are prohibited for HD patients in Japan. Although HOMA-IR is a useful clinical index of insulin resistance in practice, it has significant limitations in its use. First, HOMA-IR should be applied in a steady state of daily glycemic status. Furthermore, HOMA-IR may be inappropriately high when FPG is greater than 140 mg/dL [19]. In the present study, FPG varied from 75 to 138 mg/dL. Duration since diabetes diagnosis was averaged to be 22 ± 2 years. Among 26 diabetic patients, 12 had arterial

Table 2
Multivariate regression analysis for HOMA-IR

	Coefficient	*t*	*P*
Age	−0.005	0.31	.75
Sex	−0.20	0.52	.60
HD duration	−0.06	1.70	.09
BMI	0.02	0.24	.81
AI	−0.80	2.12	.04
SBP	0.004	0.35	.72
DBP	−0.01	0.92	.36
HR	−0.02	1.34	.18
DM	0.66	1.98	.05
FC	0.04	1.35	.18
Ox-LDL	0.22	2.30	.02
LPL	−0.004	0.24	.81

R^2 = 0.32, F = 2.7, P = .005, *df*(12,68). AI indicates angiotensin inhibition; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; DM, diabetes mellitus.

Table 3
Multivariate regression analysis for ABI

	Coefficient	*t*	*P*
Age	−0.009	2.35	.02
Sex	−0.006	0.07	.95
HD duration	−0.004	0.52	.60
BMI	0.001	0.06	.95
AI	0.085	1.03	.31
SBP	0.001	0.17	.86
DBP	0.001	0.12	.90
HR	−0.006	0.87	.39
DM	−0.28	3.33	.001
FC	−0.002	0.34	.73
Ox-LDL	−0.02	1.87	.06
LPL	0.002	0.44	.66

R^2 = 0.31, F = 2.6, P = .007, *df*(12,68).

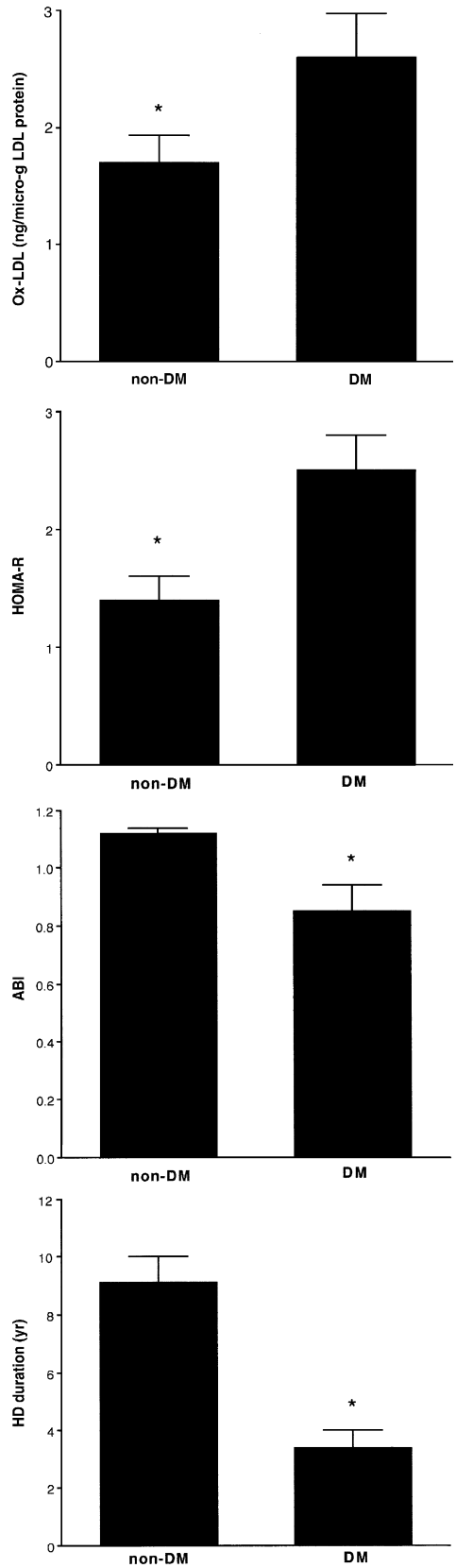

Fig. 1. Comparison of oxidized low-density lipoprotein (ox-LDL), homeostasis model assessment method (HOMA-IR), ankle-brachial pressure index (ABI), and hemodialysis (HD) duration between diabetic (DM) and nondiabetic patients. *$P < .05$.

calcification, whereas 11 of 55 nondiabetic patients had arterial calcification.

The relationship of ABI or HOMA-IR with patient profiles was characterized in a cross-sectional study. At first, multivariate regression analysis for HOMA-IR or ABI was performed using age, sex, HD duration, body mass index (BMI), angiotensin inhibition, blood pressure, heart rate, and diabetes ox-LDL, LPL, and FC levels as independent variables. Furthermore, comparisons of HOMA-IR and ABI were carried out between diabetic and nondiabetic patients. Patients who took angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) were considered under angiotensin inhibition. In addition, the effects of angiotensin inhibition on HOMA-IR and ABI were assessed in nondiabetic patients.

The relationship between HOMA-IR and cardiovascular events requiring hospitalization was assessed in a prospective study. HOMA-IR was used as an index of insulin resistance in accordance with the criteria set forth by the Japan Diabetes Society [19]. Patients were divided into 3 groups according to their HOMA-IR. The first group included those who did not have insulin resistance (HOMA-IR <1.6); the second group, those patients with insulin resistance (1.6 < HOMA-IR < 2.5); and the third group, those patients with overt insulin resistance (HOMA-IR >2.5). The relationship between cardiovascular events and ABI was also examined.

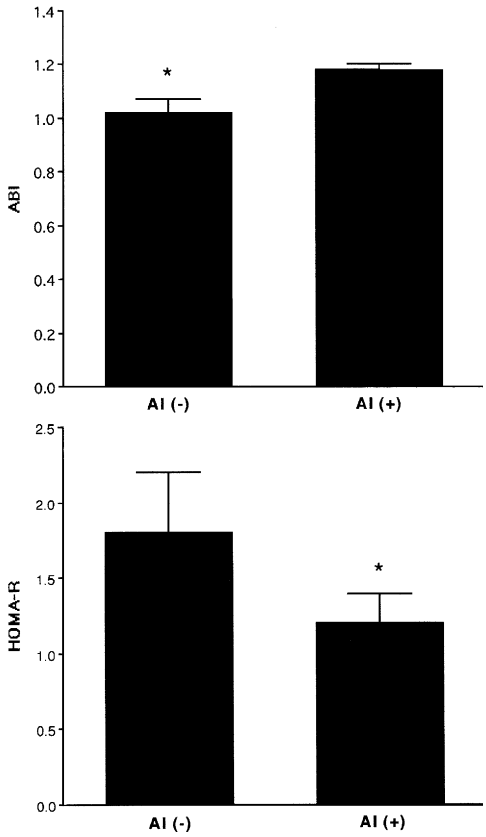

Fig. 2. Comparison of HOMA-IR and ABI in nondiabetic patients with and without angiotensin inhibition (AI). *$P < .05$.

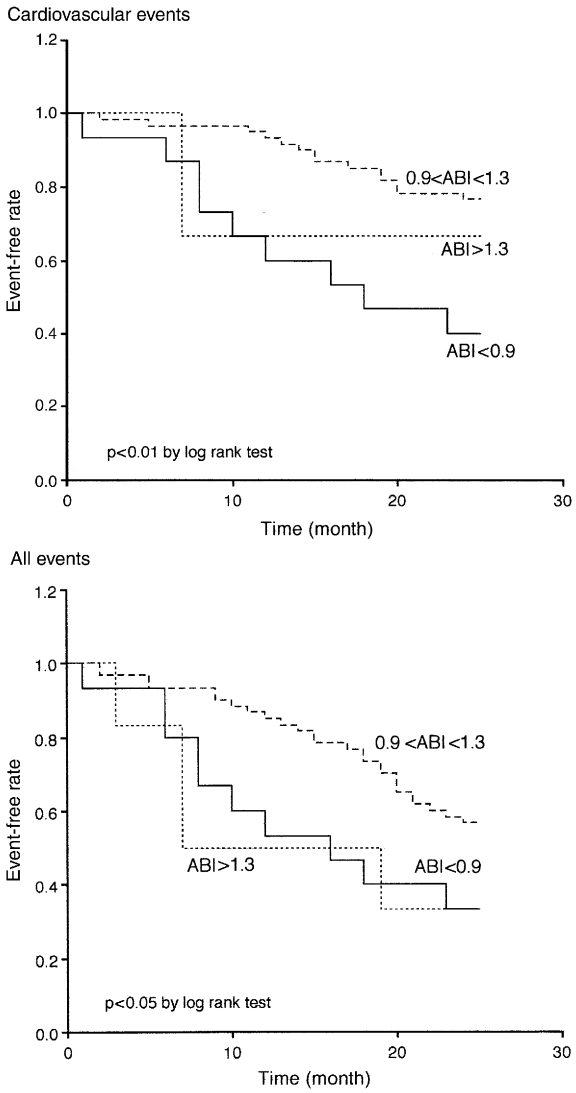

Fig. 3. Relationship of ABI with cardiovascular and all events requiring hospitalization.

Patients were divided into 3 groups [23-25]. The first group included those patients whose ABI was lower than 0.9; the second group, those patients whose ABI was greater than 0.9 but less than 1.3; and the third group, those patients with ABI greater than 1.3. ABI may often give a falsely high value in the patients possessing severe vascular disease with arterial calcification [23,24]. We also examined the relationships of HOMA-IR and ABI to the incidence of hospitalization from all events.

Data were expressed as mean ± SEM. Statistical analysis was performed using the Mann-Whitney test and Kaplan-Meier test followed by log-rank test [2,26]. A P value less than .05 was considered statistically significant.

3. Results

A total of 81 patients were enrolled. The mean age and the mean HD duration were 59 ± 1 and 7 ± 1 years, respectively, at the time of study entry. Dry weight and BMI were 58 ± 1 kg and 21.8 ± 0.8 kg/m^2, respectively. The mean blood pressure and heart rate were 139 ± 2/75 ± 2 mm Hg and 73 ± 1 beats/min, respectively. The mean ABI and HOMA-IR were 1.04 ± 0.04 and 1.76 ± 0.16, respectively. The mean values of FC, ox-LDL, and LPL levels were 26 ± 1 μmol/L, 2.0 ± 0.2 ng/μg LDL, and 132 ± 3 ng/mL, respectively. As shown in Table 1, 15 patients (7 nondiabetic and 8 diabetic) had ABIs less than 0.9, and 6 patients (1 diabetic and 5 nondiabetic) had ABIs greater than 1.3. Moreover, 48 patients (40 nondiabetic and 8 diabetic) exhibited a HOMA-IR of less than 1.6, and 18 patients (6 nondiabetic and 12 diabetic) showed overt insulin resistance (HOMA-IR >2.5). Sixty patients received treatment with angiotensin blockade with either ACEIs (in milligrams per day: captopril, 12.5-50; temocapril, 2-4; trandolapril, 2; and imidapril, 5) or ARBs (in milligrams per day: losartan, 50-100; valsartan, 80; and

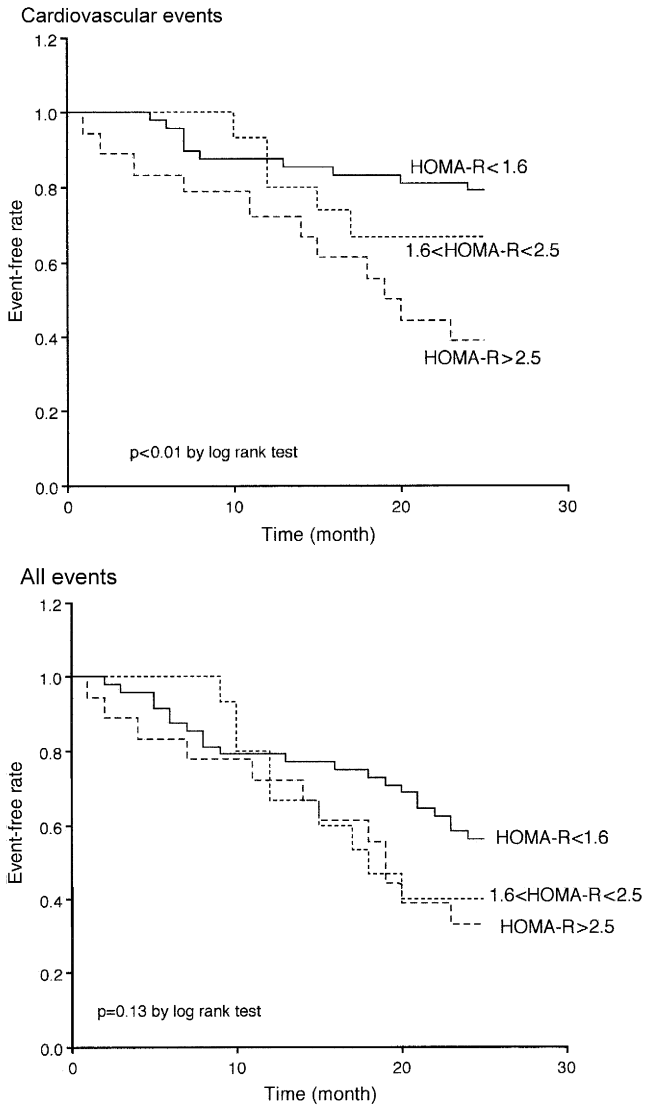

Fig. 4. Relationship of HOMA-IR with cardiovascular and all events requiring hospitalization.

candesartan, 4). Of note, only 4 of 26 diabetic patients took neither ACEI nor ARB.

As shown in Table 2, multivariate regression analysis indicated that HOMA-IR was related inversely to angiotensin inhibition (−0.80 ± 0.38, $P < .05$, n = 81) and positively to ox-LDL level (0.22 ± 0.10 ng/μg LDL, $P < .05$) and the presence of diabetes (0.66 ± 0.33, $P < .05$). ABI was inversely correlated with age (−0.009 ± 0.004/y, $P < .05$, n = 81) and the presence of diabetes (−0.28 ± 0.09, $P = .001$; Table 3). Although some patients showed FC and/or LPL lower than the respective reference range, neither FC nor LPL correlated with HOMA-IR.

Diabetic patients (n = 26) showed higher HOMA-IR (2.5 ± 0.3 vs 1.4 ± 0.2, $P < .05$) compared with nondiabetic patients (n = 55), although their BMIs were similar (22.3 ± 0.5 vs 21.5 ± 0.4 kg/m^2; Fig. 1). Thus, they were not obese. Furthermore, diabetic patients possessed lower ABI (0.85 ± 0.09 vs 1.12 ± 0.02, $P < .01$) and shorter HD duration (3 ± 1 vs 9 ± 1 years, $P < .01$) than nondiabetic patients (Fig. 1). Although the mean age of diabetic patients (60 ± 2 years) was similar to that of nondiabetic patients (59 ± 2 years), ox-LDL level was higher in diabetic patients (2.6 ± 0.4 vs 1.7 ± 0.2 ng/μg LDL, $P < .05$). FPG level was higher in diabetic patients than in nondiabetic patients (117 ± 2 vs 96 ± 1 mg/dL, $P < .0001$), and the mean glycosylated hemoglobin level was 5.8% ± 0.2% in the former group.

Fig. 2 shows the effects of angiotensin inhibition on HOMA-IR and ABI. In nondiabetic patients, the patients who took angiotensin inhibitors (n = 38) had lower HOMA-IR (1.2 ± 0.2 vs 1.8 ± 0.4, $P < .05$) than those who did not (n = 17), but BMI was similar between the 2 groups (21.4 ± 0.4 vs 21.8 ± 0.7 kg/m^2). Angiotensin inhibition resulted in higher ABI (1.18 ± 0.02 vs 1.02 ± 0.05, $P < .05$), whereas HD duration did not differ between the 2 groups (9 ± 1 vs 10 ± 2 years). Although age (63 ± 2 years) and ox-LDL level (2.1 ± 0.4 ng/μg LDL) of patients without angiotensin inhibition tended to exceed those with angiotensin inhibition (57 ± 2 years and 1.5 ± 0.2 ng/μg LDL, respectively), the difference was not statistically significant ($P = .08$ and $P = .11$).

The relationship between ABI and clinical events is shown in Fig. 3. The patients were followed up for 2 years. Patients with intermediate ABI (0.9 < ABI < 1.3) showed a lower incidence of hospitalization from cardiovascular ($P < .01$) and all events ($P < .05$). Cardiovascular events included cerebrovascular accidents, coronary heart disease, heart failure, peripheral arterial disease, and shunt occlusion. The other causes of hospitalization included sepsis, hepatic encephalopathy, hematopoietic dysplasia, traumatic fracture, carpal tunnel syndrome, spinal canal stenosis, parathyroidectomy, gastric ulcer and carcinoma, colon carcinoma, hepatocellular carcinoma, thyroid carcinoma, renal cell carcinoma, benign prostate hypertrophy, and cataract.

The relationship between HOMA-IR and clinical events is shown in Fig. 4. Although patients with high HOMA-IR (>2.5) failed to show a difference in the incidence of hospitalization due to all causes, they showed significantly higher incidence of cardiovascular events requiring hospitalization than the other 2 subgroups ($P < .01$). During 2 years of follow-up, 4 patients died in this cohort; 2 were diabetic and 2 were not. One male diabetic patient died of myocardial infarction, and 1 female diabetic died of peripheral arterial disease. Causes of death in the 2 nondiabetic male patients were heart failure and sepsis. Survival analysis using Kaplan-Meier test did not show a significant difference among HOMA-IR or ABI subgroups, probably because only a small number of deaths occurred.

4. Discussion

The most important finding in the present study is that many HD patients have HOMA-IR exceeding the reference range (Table 1). Although the precise reasons why many HD patients possess insulin resistance are not clear from the present study, multiple factors could contribute to the high prevalence of insulin resistance among this population. First, there may be a genetic predisposition of diabetic patients to insulin resistance. Indeed, the present data indicate that nondiabetic patients have lower HOMA-IR than diabetic patients, although they are not obese. In addition, previous findings demonstrated that some HD patients have low carnitine levels, inducing muscle fatigue, worsening of anemia, and heart failure [16]. Because carnitine helps mitochondrial oxidation, its deficiency may cause insulin resistance [18]. Recent investigations demonstrated that overexpression of LPL elicits insulin resistance [17]. LPL is altered in HD patients who are repeatedly exposed to heparin [21]. Furthermore, we previously reported that HD patients were exposed to excessive oxidative stress and manifested high level of ox-LDL [2]. Oxidized LDL contains lysophosphatidylcholine, which activates protein kinase C that phosphorylates the serine residue of insulin receptor substrate-1, thereby preventing insulin-induced tyrosine phosphorylation and then inhibiting signal transduction of insulin [27]. More importantly, this mechanism is shared with angiotensin II. The present results that ox-LDL correlates with HOMA-IR suggest that oxidative stress contributes to insulin resistance in HD patients.

We previously reported, using simple regression analysis, that ABI was related inversely to age [2]. Consistent with this, using multivariate regression analysis, we reveal in the present study that ABI correlated with both age and the presence of diabetes. Hyperglycemia is a well-known risk factor for atherosclerosis. In the present study, FPG and ox-LDL were higher in diabetic than in nondiabetic patients. In contrast, it was reported that in vitro LDL oxidizability was normal or even lower in patients with type 2 diabetes mellitus [28]. However, glucose acts as a scavenger of nitric oxide, a strong antioxidant [29]. Thus, hyperglycemia may directly contribute to an increase in oxidative stress.

Furthermore, our recent data implicated that compared with nondiabetic patients, diabetic patients manifested a faster increase in pulse wave velocity, a marker of arterial stiffness that is a characteristic feature of atherosclerosis [3]. Recently, the number of diabetic patients who need dialysis treatment has increased, and, since 1998, diabetic nephropathy has been a primary disease that required initiation of dialysis therapy in Japan [30]. In addition, diabetic patients survive for a shorter period than nondiabetic patients after the initiation of dialysis therapy. The database of the Japanese Society of Dialysis Therapy indicates that 53% of patients who had dialysis therapy due to end-stage renal failure from chronic glomerulonephritis survived for 10 years, whereas only 26% of those with diabetic nephropathy survived more than 10 years. These trends seem to account for the present observations that diabetic patients showed shorter HD duration.

Our recent data on patients with renal hypertension with mild renal insufficiency (1.2 mg/dL < serum creatinine level < 2.0 mg/dL) suggest that patients with a history of cardiovascular disease manifest higher cardiovascular morbidity than those without [31]. As noted, ABI may often give a falsely high value in the patients who have severe vascular disease with arterial calcification [23,24], possibly accounting for the fact that patients with ABI >1.3 needed more hospitalization than those with intermediate ABI (from 0.9 to 1.3). The present results indicate that HD patients with lower ABI experience more cardiovascular events requiring hospitalization. Ono et al demonstrated that low ABI is predictive of both cardiovascular and all-cause deaths in HD patients [24]. Our present results also indicate that patients with lower ABI experience higher incidence of clinical events from all causes; this observation is in agreement with that previously reported by Ono et al [24]. Cardiovascular events comprised 62% of all events in the present study. These observations suggest that preexisting vascular injury predicts cardiovascular events in patients with renal disease, regardless of the magnitude of renal function impairment.

The present data indicate that high HOMA-IR is related to an increase in incidence of cardiovascular events. These data are compatible with the observations by Shinohara et al [32], who demonstrated that HD patients with HOMA-IR of greater than 1.6 have higher cardiovascular death than those with HOMA-IR of less than 1.6. Moreover, our recent results suggest that in addition to antioxidants, angiotensin inhibition was required to arrest progressive elevations of pulse wave velocity in HD patients [3]. Angiotensin inhibition could make insulin sensitivity better via various pathways. Indeed, the present findings suggest that angiotensin inhibition is inversely related to HOMA-IR in all 81 patients in this study. Angiotensin enhances the expression of nicotinamide adenine dinucleotide phosphate (reduced form) oxidase [33], presumably increasing ox-LDL level and then insulin resistance. However, multivariate regression analysis showed that angiotensin inhibition and ox-LDL independently contributed to HOMA-IR. Alternatively, angiotensin directly activates protein kinase C and phosphorylates the serine residue of insulin receptor substrate-1, thereby interacting with insulin signaling [14]. Together, these observations suggest that the former mechanism might play a small role in decrease of HOMA-IR associated with angiotensin inhibition. Finally, our results imply that nondiabetic patients with angiotensin inhibition have lower HOMA-IR and higher ABI than those without angiotensin inhibition and suggest that angiotensin inhibition improves insulin resistance in HD patients, thereby presumably retarding the progression of vascular injury.

In summary, our data indicate that insulin resistance prevails in HD patients, and that ox-LDL level is related to HOMA-IR in this population. The present results suggest that angiotensin inhibition improves insulin resistance, especially in nondiabetic HD patients. Finally, our findings provide evidence that insulin resistance predicts cardiovascular events in HD patients.

Acknowledgment

The authors would like to thank Eriko Oshima, Hiroshi Tagai, Miki Ito, Shingo Iwasaki, and Kenji Takahashi for their excellent technical assistance.

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