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Insulin Resistance and Left Ventricular Mass in Non-Diabetic Hemodialysis Patients

Sebnem Karakan, MD[1]; Siren Sezer, MD[1]; and F. Nurhan Özdemir Acar, MD[2]

[1]Department of Nephrology, Baskent University, Ankara, Turkey; and [2]Department of Nephrology, Baskent University, İstanbul, Turkey

ABSTRACT

BACKGROUND: Insulin resistance (IR) is frequently recognized in patients with uremia, and it is thought that IR has a basic role in the pathogenesis of cardiovascular disease.

OBJECTIVE: To evaluate the effect of IR on cardiovascular risk in non-diabetic patients receiving hemodialysis (HD).

METHODS: We performed a cross-sectional observational study that comprised 186 non-diabetic patients receiving HD (95 men; mean [SD] age, 46.4 [10.8] years; age range, 35–60 years) who had been receiving HD for 7.3 (3.5) years. Demographic variables and laboratory values were recorded. Insulin resistance was determined using the Homeostatic Model Assessment (HOMA), and the left ventricular mass index (LVMI) was calculated via echocardiography.

RESULTS: According to HOMA-IR levels, patients were categorized as having IR (HOMA-IR score $\geq$2.5; $n = 53$) or not having IR (HOMA-IR score $<$2.5; $n = 133$). Insulin resistance was determined in 28.4% of study patients. Compared with the non-IR group, the IR group had been receiving HD longer; had greater body mass index; and had higher serum creatinine, uric acid, triglyceride, insulin, and C-reactive protein concentrations, leukocyte count, and LVMI ($P < 0.05$). Patients with increased LVMI had significantly higher body mass index, systolic blood pressure, serum cholesterol and C-reactive protein concentrations, and HOMA score. At multivariate analysis, systolic blood pressure ($\beta = 0.22$; $P = 0.03$) and HOMA score ($\beta = 0.26$; $P = 0.01$) affected LVMI.

CONCLUSIONS: Insulin resistance and hypertension are independent risk factors for left ventricular hypertrophy in non-diabetic patients with uremia who are receiving HD. Further studies are needed to indicate the benefits of improving IR for cardiovascular mortality in this subgroup of patients with uremia. (*Curr Ther Res Clin Exp.* 2012;73:165–173) © 2012 Published by Elsevier HS Journals, Inc.

KEY WORDS: hemodialysis, insulin resistance, ventricular hypertrophy.

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INTRODUCTION

The process of cardiovascular damage starts very early in patients with chronic kidney disease, and the damage progresses rapidly with advanced kidney dysfunction.[1,2] Insulin resistance (IR) occurs frequently in patients with uremia, and it is thought that it has a basic role in the pathogenesis of cardiovascular disease in end-stage renal disease (ESRD).[3–7] Insulin resistance may be involved in the pathogenesis of atherosclerosis, hypertension, and dyslipidemia. Moreover, in patients with ESRD, there is premature aging of the vascular tree. Endothelial dysfunction in patients receiving dialysis therapy has negative effects on left ventricular structure and function.[7] The relationship between IR, which is a proinflammatory state, and left ventricular mass index (LVMI) has not been investigated in patients receiving hemodialysis (HD). To date, no study is available in the literature that examined the possible relationship between IR and LVMI in non-diabetic patients receiving HD.

METHODS

PATIENTS

We performed a cross-sectional observational study in patients receiving HD to evaluate the effect of IR on LVMI. The study comprised 186 non-diabetic patients (95 men; mean [SD] age, 46.4 [10.8] years; age range, 35–60 years) who had been receiving HD for 7.3 (3.5) years. Inclusion criteria were age ≥18 years and duration of previous dialysis ≥6 months. Exclusion criteria were diabetes mellitus, cardiac failure, acute myocardial infarction, comorbidity with malignancy, and acute infective disorders in the 3 months before inclusion in the study. No patients were obese (body mass index, 20–29), and none were malnourished. The causes of ESRD were hypertension in 52 patients (28%), chronic glomerulonephritis in 31 patients (16%), polycystic kidney disease in 26 patients (14%), interstitial nephritis in 17 patients (10%), and other or unknown cause in 60 patients (32%). Hemodialysis was performed 3 times a week (4 hours per session), with an average blood flow rate of 300 to 350 mL/min, dialysate flow of 500 mL/min, and mean Kt/V maintained at >1.2 during the study. The study protocol was approved by the local scientific ethics committee, and informed consent was obtained from each patient.

Demographic variables (age, sex, cause of ESRD, duration of HD, and anthropometric measurements) were recorded. After an overnight fast in a mid-week day, pre-dialysis blood samples were drawn for analysis of laboratory values (**Table I**). The insulin level was measured via electroimmunoassay using a Modular Analytics E170 insulin kit (Roche Diagnostics GmbH, Mannheim, Germany), and glucose was measured via spectrophotometry using a hexokinase assay. Insulin resistance was characterized using the Homeostasis Model Assessment Method (HOMA-IR) and calculated as fasting insulin (U/mL) × fasting glucose (mmol/L)/22.5.[8] Patients were classified as HOMA-IR(+) if their HOMA score was ≥2.5. Demographic, clinical, and biochemical characteristics of these patients are given in **Table I**. Nursing staff measured systolic and diastolic blood pressure using standard mercury sphygmomanometers on the right arm of seated participants who had rested for at least 5 minutes.

Table I. Demographic, clinical, and biochemical characteristics of the study patients.

Variable	Value
No. of patients, male/female	95/91
Age, y	46.4 (10.8); 35–60
Blood pressure, mm Hg	
Systolic	124.7 (28.1); 98–162
Diastolic	79.1 (13.7); 60–110
Body mass index	25.2 (4.9); 20–30
Hemodialysis duration, y	7.3 (3.5); 3.8–10.8
Renal diagnosis, No. (%)	
Hypertension	52 (28)
Chronic glomerulonephritis	31 (16)
Polycystic kidney disease	26 (14)
Interstitial nephritis	17 (10)
Other or unknown	60 (32)
Blood urea nitrogen, mg/dL	51.7 (13.5); 26–64
Creatinine, mg/dL	8.4 (2.5); 5.3–10.8
Glucose, mg/dL	88.1 (32.3); 60–113
Uric acid, mg/dL	6.0 (1.9); 3.7–8.0
Total cholesterol, mg/dL	185.7 (50.0); 96.0–267.0
Low-density lipoprotein cholesterol, mg/dL	97.9 (64.7); 80–130
Triglycerides, mg/dL	213.6 (198.9); 51.0–442.0
C-reactive protein, mg/dL	10.9 (10.1); 0–43
Insulin, IU/L	12.3 (11.4); 0.9–23.7
Hemoglobin, g/dL	11.4 (1.4); 8.3–12.8
Leukocyte count, 10^3/mL	7.4 (2.4); 3.5–9.8
Platelet count (/mL)	254.6 (74.2); 115–334
Kt/V, wk	1.96 (0.44)
Ejection fraction, %	48.7 (8.4); 20–60
Left ventricular internal dimension, mm	151.8 (41.6)
Left ventricular mass index, g/m^2	137.6 (24.1); 113–163
HOMA-IR score	2.6 (1.8); (0.8–4.4)

Unless otherwise indicated, values are given as mean (SD); range.

Weight, height, and waist circumference were determined for each patient. Waist circumference was measured at the narrowest diameter between the costal margin and the iliac crest. Height (in meters) and weight (in kilograms) were measured with the patient dressed in light clothing and without shoes. Several indicators of adiposity were calculated from these measurements. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters.

ECHOCARDIOGRAPHY

Echocardiographic examinations were performed using 2-dimensional, M-mode, pulse-wave Doppler, and tissue Doppler echocardiography by using a sonographic system (Hewlett Packard Sonos 7500; Philips Medical Systems, Andover, Massachusetts) with a 2.8-MHz probe. Conventional echocardiography measurements (M-mode and conventional pulse-wave Doppler) were determined according to guidelines of the American Society of Echocardiography.[9] Left ventricular mass (LVM) was calculated using the Devereux formula[10]: LVM (g) = 0.8 × [1.04 × (IVST + LVID + LPWT)3 – (LVID)3 + 0.6], where IVST = interventricular septal thickness, LVID = left ventricular internal dimension, and LPWT = left posterior wall thickness. The left ventricular mass index (LVMI) was calculated using the formula LVM/(height)2.7.[10] The ratio of early diastolic–late diastolic mitral inflow velocities was measured. Tissue Doppler imaging was performed using the apical 4-chamber view, and the images were digitized. Myocardial velocity profiles of the lateral mitral annulus were obtained by placing a 6-mm sample at the junction of the mitral annulus and the lateral myocardial wall.

STATISTICAL ANALYSES

Statistical analysis was performed using SPSS for Windows (version 13.0; SPSS, Inc, Chicago, Illinois). All data are given as mean (SD). Geometric means for all log-normally distributed continuous variables were calculated and reported with 95% confidence intervals, and duration of HD as median values and ranges. If possible, data were logarithmically transformed to achieve a normal distribution. Normally distributed measurements were evaluated using an independent sample *t* test and reported as mean (SD), and nonnormally distributed data were evaluated using the Mann-Whitney *U* test and reported as median and minimal–maximal values. Factors showing a linear correlation with insulin resistance ($P \leq 0.05$) were included in the analysis. Pearson or Spearman coefficients were used. The Mann-Whitney rank sum *U* test or Student *t* test were used for statistical analysis to compare differences between groups. Multiple regression analysis was used to determine independent factors affecting the dependent variable. $P \leq 0.05$ was considered significant.

RESULTS

PATIENT CHARACTERISTICS AND COMPARISON BETWEEN PATIENTS WITH AND WITHOUT IR

In the present study, 186 non-diabetic patients receiving HD were assessed for IR. The median (interquartile range) HOMA-IR score was 3.33 (1.94) (range, 1.39–5.27). According to HOMA-IR scores, patients were classified as having IR (HOMA-IR score ≥2.5; $n = 53$) or not having IR (HOMA-IR score <2.5; $n = 133$). Insulin resistance was found in 28.4% of all study patients. The IR group, compared with the non-IR group, had been receiving HD longer (6.8 [3.2] years vs 4.2 [1.1]years; $P < 0.01$); had greater BMI (26.1 [3.9] vs 24.3 [4.3]; $P < 0.01$); had higher serum concentrations of creatinine (8.3 [2.1] mg/dL vs 7.1 [2.7] mg/dL; $P = 0.04$), uric acid (6.8 [1.2] mg/dL vs 5.6 [1.9] mg/dL; $P < 0.01$), triglycerides (218.2

Table II. Comparison of clinical and biochemical variables in patients with and without IR.

Variable	With IR (n = 53)	Without IR (n = 133)	P
Age, y	48.9 (15.4)	47.7 (13.3)	NS
No. of patients, male/female	21/32	74/59	NA
Duration of HD, y, median (SD)	6.8 (3.2)	4.2 (1.1)	0.01
Body mass index	26.2 (3.9)	24.3 (4.3)	0.01
Creatinine, mg/dL	8.3 (2.1)	7.1 (2.7)	0.04
Uric acid, mg/dL	6.8 (1.2)	5.6 (1.9)	0.01
Triglycerides, mg/dL	218.2 (42.2)	187.4 (36.9)	0.01
C-reactive protein, mg/L	8.4 (7.2)	4.7 (4.1)	0.03
Leukocyte count, 10^3/mL	8.6 (1.8)	7.8 (2.1)	0.02
LVMI, g/m^2	146.3 (34.2)	132.2 (36.9)	0.01

HD = hemodialysis; IR = insulin resistance; LVMI = left ventricular mass index; NA = not applicable; NS = not significant.
Unless otherwise indicated, values are given as mean (SD).

[42.2] mg/dL vs 187.4 [36.9] mg/dL; $P < 0.01$), insulin (16.4 [7.2] IU/L vs 8.24 [2.61] IU/L; $P < 0.01$), and C-reactive protein (CRP) (8.4 [7.2] mg/dL vs 4.7 [4.1] mg/dL; $P = 0.03$); had a higher leukocyte count (8.6 [1.8] $\times$ 10^3/mL vs 7.8 [2.1] $\times 10^3$/mL; $P = 0.02$); and had greater LVMI (146.3 g/m^2 [34.2] vs 132.2 [36.9] g/m^2; $P < 0.01$) (Table II).

Correlations Between IR and LVMI

Mean (SD) LVMI was calculated as 137.6 (24.1). Data for LVMI were not normally distributed. Pearson correlation analysis was performed, and BMI ($r = 0.48$; $P = 0.01$), systolic blood pressure ($r = 0.62$; $P = 0.04$), and HOMA score ($r = 0.49$; $P = 0.03$) were positively correlated with LVMI, whereas hemoglobin ($r = -0.41$; $P = 0.02$) and ejection fraction ($r = -0.29$; $P = 0.04$) were negatively correlated with LVMI. Patients were divided into 2 groups according to median (SD) LVMI value (137.6 [24.1] g/m^2). Group 1 had low values (125.7 [24] g/m^2), and group 2 had high values (142.5 [16.8] g/m^2). Compared with patients in group 1, those in group 2 had significantly higher BMI ($P < 0.01$), systolic blood pressure ($P = 0.02$), and serum total cholesterol ($P = 0.04$) and CRP ($P = 0.03$) concentrations, and HOMA scores ($P = 0.03$).

At multiple linear regression analysis, we further explored age; HD duration; creatinine, uric acid, total cholesterol, CRP, and insulin concentrations; and HOMA scores as independent variables. It become apparent that systolic blood pressure ($\beta = 0.22$; $P = 0.03$) and HOMA score ($\beta = 0.26$; $P = 0.01$) affected LVMI (Table III).

DISCUSSION

Insulin resistance develops inevitably in patients with impaired renal function, and a high prevalence of IR has been found in patients with ESRD.[11–14] This study revealed

Table III. Stepwise linear regression analysis with left ventricular mass index as dependent variable.*

	Left Ventricular Mass Index	
Independent Variable	β	*P*
Age, y	0.13	NS
HD duration, y	0.12	NS
Blood pressure, mm Hg		
Systolic	0.22	0.03
Diastolic	0.19	NS
Total cholesterol, mg/dL	−0.191	NS
LDL cholesterol, mg/dL	0.16	NS
C-reactive protein, mg/L	0.17	NS
HOMA	0.26	0.01
Ejection fraction, %	−0.53	NS

HOMA = Homeostatic Model Assessment; LDL = low-density lipoprotein; NS = not significant.
*$n = 186$; $r^2 = 0.41$.

that IR, as measured via HOMA, is related to cardiovascular risks in non-diabetic patients receiving HD.

Various techniques have been previously used to assess IR and glucose tolerance in renal disease, including euglycemic insulin clamp, HOMA-IR score, oral or intravenous glucose tolerance testing, and fasting insulin concentrations.[15–20] We found the mean HOMA-IR score was 1.46 in non-diabetic patients receiving HD. This was consistent with the literature: 3 different studies reported mean HOMA-IR scores as 1.16, 1.23, and 1.40, respectively.[21–23] Our result is in agreement with the finding of Ramos et al.[24] Recent evidence has suggested that inflammation might be an important mechanism contributing to IR.[25] In the present study, inflammatory markers such as serum CRP and leukocyte count were correlated with the presence of IR. Chronic inflammatory response may be another mechanism. Cytokines secreted from adipocytes such as tumor necrosis factor-α and leptin were considered to have an important role in the development of IR in patients with uremia.[26] Insulin resistance is thought to cause endothelial inflammation, primarily via nitric oxide (NO) depletion and increased reactive oxygen species.[27–29] Subclinical elevation of serum CRP concentration in patients receiving HD may reflect microvascular inflammation induced by IR, which is likely to lead to microcirculatory disturbances in the heart. The present study also documents the close relationship between IR and uric acid concentration. Hyperuricemia has an important role in IR via its effect in lowering the NO level and also possibly by a direct effect of uric acid on adipocytes.[30]

Our analyses suggested that IR was the predominant determinant of left ventricular mass. Tissue resistance to insulin is the primary cause of IR in ESRD.[31] Insulin resistance may be linked to vascular endothelial dysfunction, which may be largely a

consequence of acquired defects of NO synthesis and intracellular signaling.[32] Endothelial dysfunction linked to IR is believed to take part in microcirculatory disturbances in the heart and to compromise myocardial adenosine triphosphate synthesis in patients with ESRD.[33–36] Because myocardial adenosine triphosphate content deeply affects left ventricular wall motion, a combination of IR and this derangement may aggravate left ventricular dysfunction. At multiple regression analysis, LVMI was strongly associated with IR in study patients. Understanding the relationship between IR and impaired cardiac functions is important for establishment of congestive heart failure in non-diabetic patients receiving HD.

CONCLUSIONS

IR assessed via HOMA-IR is closely associated with cardiovascular risk in non-diabetic patients receiving HD. Inasmuch as IR is a reversible risk factor, reduction of IR may be a potential therapeutic target. However, randomized controlled studies are needed to clarify whether enhancing insulin sensitivity could improve cardiac performance and subsequently reduce left ventricular hypertrophy and cardiovascular mortality in ESRD.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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ADDRESS CORRESPONDENCE TO: Sebnem Karakan, MD, Nefroloji, Baskent Universitesi, ABD Bahcelievler, Ankara, Turkey 06500. E-mail: sebnemkarakan@gmail.com