Original Article

Relationship between Abdominal Fat Accumulation and Insulin Resistance in Hemodialysis Patients

Tomohito GOHDA[1)], Hiromichi GOTOH[1)], Mitsuo TANIMOTO[1)], Michiko SATO[1)], Hiroaki IO[1)], Kayo KANEKO[1)], Chieko HAMADA[1)], and Yasuhiko TOMINO[1)]

It is well known that obesity and insulin resistance are closely related to the development of type 2 diabetes. However, the exact pathogenic mechanism underlying the insulin resistance in renal disease has not been clarified. The purpose of the present study was to clarify the contribution of abdominal (visceral and subcutaneous) fat accumulation to insulin resistance and various clinical parameters, including C-reactive protein (CRP), in hemodialysis (HD) patients. Visceral and subcutaneous fat areas (VFA and SFA) were evaluated at the umbilical level by CT. Insulin resistance was estimated by the homeostasis model assessment–insulin resistance index (HOMA-IR) in 80 HD patients. Insulin resistance and CRP seemed to be closely correlated with fat-related parameters such as body mass index (BMI), VFA and SFA. HOMA-IR was positively correlated with BMI, VFA, SFA, triglycerides (TG), remnant-like particle (RLP)-cholesterol and CRP in simple regression analysis. In multiple stepwise regression analysis, SFA and RLP-cholesterol were predominant determinants of HOMA-IR in HD patients. Furthermore, CRP was positively correlated with BMI, VFA, SFA, TG, high-density lipoprotein (HDL)-cholesterol, atherosclerosis index (AI), immunoreactive insulin (IRI) and HOMA-IR in simple regression analysis. In multiple stepwise regression analysis, VFA and HDL-cholesterol were predominant determinants of CRP in HD patients. In conclusion, insulin resistance and CRP were related to fat-related parameters such as BMI, VFA and SFA in HD patients. Furthermore, the contribution of SFA to insulin resistance was much higher than that of VFA, while the opposite relation was recognized for CRP. (*Hypertens Res* 2008; 31: 83–88)

***Key Words*: abdominal adipose tissue, obesity, insulin resistance, C-reactive protein, hemodialysis**

Introduction

Obesity and inflammation or obesity and insulin resistance are closely related (*1*, *2*). Overweight individuals commonly demonstrate elevated levels of inflammatory molecules such as C-reactive protein (CRP). High levels of inflammation have been implicated in the pathogenesis of cardiovascular disease (CVD). CRP, an acute-phase reactant protein and a marker of systemic inflammation, is known to be an important predictor of future cardiovascular events or mortality (*3*, *4*). Adipose tissue secretes proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). These cytokines stimulate the production of CRP. About 30% of the total circulating level of IL-6 originates from adipose tissue in healthy Caucasians (*5*). Thus, adipose tissue is an important factor for the CRP in healthy individuals.

Insulin resistance is often observed in patients with renal insufficiency. Accumulation of uremic toxins and metabolic acidosis have been hypothesized as the major causes of the insulin resistance observed in these patients (*6*, *7*). Since most hemodialysis (HD) patients are maintained at an appropriate

From the [1)]Division of Nephrology, Department of Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan.

Address for Reprints: Yasuhiko Tomino, M.D., Division of Nephrology, Department of Internal Medicine, Juntendo University School of Medicine, 2–1–1 Hongo, Bunkyo-ku, Tokyo 113–8421, Japan. E-mail: yasu@med.juntendo.ac.jp

Received April 30, 2007; Accepted in revised form August 5, 2007.

Table 1. Characteristics of Hemodialysis Patients

Characteristics	Mean±SD	DM	Non-DM	
Number	80	25	55	
Age (years)	64.2±12.2	67.1±9.9	62.9±13.1	n.s.
Sex (male/female)	44/36	15/10	29/26	n.s.
Duration of HD (months)	68.0±65.0	38.0±45.2	80.8±68.2	<0.01
BMI (kg/m)	20.1±2.9	21.2±3.2	19.6±2.6	<0.05
VFA (cm^2)	91.0±71.6	98.6±77.6	87.9±68.3	n.s.
SFA (cm^2)	97.6±79.7	108.2±81.1	93.2±78.3	n.s.
Serum total cholesterol (mg/dL)	183.5±37.1	193.1±34.0	179.2±37.9	n.s.
Serum HDL cholesterol (mg/dL)	53.6±15.0	54.2±14.3	53.4±15.5	n.s.
AI	2.6±1.1	2.7±0.9	2.6±1.2	n.s.
Serum triglyceride (mg/dL)	98.7±42.1	105.1±43.6	95.9±41.5	n.s.
Serum RLP-cholesterol (mg/dL)	4.4±2.3	5.4±3.1	4.0±1.8	<0.05
Fasting plasma glucose (mg/dL)	96.8±22.1	116.6±23.1	87.3±10.3	<0.0001
Immunoreactive insulin (μU/mL)	6.3±4.0	7.3±3.1	5.9±4.3	n.s.
HOMA-IR	1.6±1.1	2.1±1.1	1.3±1.0	<0.005
CRP (mg/dL)	0.09±0.10	0.11±0.07	0.09±0.11	n.s.

DM, type 2 diabetes; HD, hemodialysis; BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; HDL, high-density lipoprotein; AI, atherosclerosis index; RLP, remnant-like particle; IRI, immunoreactive insulin; HOMA-IR, homeostasis model assessment–insulin resistance index; CRP, C-reactive protein.

body mass index (BMI), insulin resistance might be determined in part not only by BMI but also by abdominal fat distribution. Some reports have demonstrated that accumulation of visceral adipose tissue (VAT) is related to insulin resistance, while that of subcutaneous abdominal fat (SAT) is generally not related to insulin resistance (*8*, *9*). HD improves uremic-induced glucose intolerance to some extent. However, the exact pathogenic mechanism underlying insulin resistance in renal disease has not been clarified.

The purpose of the present study was to clarify the contribution of abdominal (visceral and subcutaneous) fat tissue accumulation to insulin resistance and various clinical parameters, including CRP, in HD patients.

Methods

Subjects

Eighty HD patients (age 64.2±12.2 years, mean±SD; male/female 44/36; duration of HD, 68.0±65.0 months) were recruited for this study. The reason for the renal insufficiency necessitating HD was chronic glomerulonephritis in 27 patients, diabetic nephropathy in 25, nephrosclerosis in 17, polycystic kidney disease in 5, pregnancy-induced hypertension in 2, vesico-ureteric reflux in 1, Alport syndrome in 1 and unknown cause in 2. The diabetic patients who were receiving insulin were excluded from this study. Among the 80 HD patients, 10 were receiving oral hypoglycemic agents, 65 antihypertensive agents and 8 antihyperlipidemia agents. The HD patients were maintained on a regular regimen using bicarbonate dialyzate (AK-SOLITA; Ajinomoto Pharma Co., Ltd., Tokyo, Japan) three times a week. Dry weight was determined in each case to achieve a normotensive, edema-free status based on the inferior vena cava diameter, plasma concentration of arterial natriuretic peptide and cardiothoracic ratio. Blood samples for biochemical parameters were drawn before starting HD and in a fasting state. For diabetic patients, blood samples were drawn before taking the morning oral hypoglycemic agents. Informed consent was obtained from all patients before the study onset. The study protocol was approved by the Ethics Committee of Juntendo University School of Medicine.

Measurement of Body Fat Mass

Abdominal fat distribution was determined using abdominal CT at the level of the umbilicus. CT scans were performed with the subject in the supine position using a slip ring CT scanner (Aquilion; Toshiba, Tokyo, Japan). SAT was clearly defined as the extraperitoneal fat between the skin and muscle. Intra-abdominal tissue with the same density as the SAT was defined as VAT. The subcutaneous fat area (SFA) and visceral fat area (VFA) were also measured at the level of the umbilicus.

Biochemical Analysis

BMI was calculated as the weight in kg divided by the square of the height in m. Plasma glucose and serum lipid (total cholesterol, high-density lipoprotein [HDL]-cholesterol and triglyceride) levels were measured using standard laboratory methods. The atherosclerosis index (AI) was calculated based

Table 2. Simple Correlation of BMI, VFA and SFA with Clinical Parameters in Hemodialysis Patients

Variables	BMI		VFA		SFA	
	r	*p*	*r*	*p*	*r*	*p*
Age	0.05	0.70	0.15	0.19	−0.11	0.34
Duration of HD	−0.25	<0.05	−0.12	0.32	−0.16	0.17
Total cholesterol	0.05	0.65	0.20	0.10	0.07	0.54
HDL-cholesterol	−0.12	0.29	−0.17	0.14	−0.10	0.40
AI	0.15	0.21	0.27	0.20	0.11	0.35
Triglyceride	0.15	0.19	0.44	<0.0001	0.21	0.08
RLP-cholesterol	0.06	0.61	0.29	<0.01	0.19	0.10
Fasting plasma glucose	0.02	0.83	0.03	0.79	0.02	0.86
IRI	0.58	<0.0001	0.50	<0.0001	0.71	<0.0001
HOMA-IR	0.59	<0.0001	0.48	<0.0001	0.66	<0.0001
CRP	0.23	<0.05	0.43	<0.0001	0.32	0.005

BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; HD, hemodialysis; HDL, high-density lipoprotein; AI, atherosclerosis index; RLP, remnant-like particle; IRI, immunoreactive insulin; HOMA-IR, homeostasis model assessment–insulin resistance index; CRP, C-reactive protein.

on the formula AI = (total cholesterol − HDL-cholesterol)/HDL-cholesterol. Levels of remnant-like particle (RLP)-cholesterol were measured using immunoadsorption (JIMRO II; Japan Immunoresearch Lab, Takasaki, Japan). CRP levels were measured using a commercially available kit (Auto-LIA CRP HS; Nissui, Tokyo, Japan). Plasma insulin levels were also measured by radioimmunoassay. In subjects with fasting plasma glucose levels of 170 mg/dL or less who were not receiving insulin, the insulin resistance was estimated by homeostasis model assessment (HOMA). The HOMA–insulin resistance index (HOMA-IR) was calculated with the following formula: fasting insulin (μU/mL) × fasting glucose (mg/dL)/405. This index can be used in patients with renal failure (*10*).

Statistical Analysis

Data were expressed as the means±SD. Simple regression analysis was applied to examine the relationship between BMI, VFA, SFA, CRP or HOMA-IR and various biochemical parameters. Multiple stepwise regression analysis was used to determine the contribution of various factors to HOMA-IR or CRP. A p value <0.05 was considered statistically significant. All statistical calculations were performed with StatView software.

Results

Characteristics of HD Patients

Clinical characteristics of the HD patients with type 2 diabetes mellitus (DM) and non-DM patients are summarized in Table 1. Fasting plasma glucose levels were less than 170 mg/dL in all diabetic patients. There were significant differences in the levels of serum RLP-cholesterol, fasting plasma glucose, HOMA-IR, BMI and duration of hemodialysis between the two groups. However, other clinical parameters were not significantly different between these groups.

Correlations between Fat-Related Parameters and Other Clinical Parameters

The respective relationships between BMI, VFA or SFA and clinical parameters for the HD patients are shown in Table 2. The data indicate that insulin resistance and CRP appear to have a close correlation with these fat-related parameters. Since there was no significant difference in the relationship of fat-related parameters with insulin resistance and CRP between diabetic and non-diabetic HD patients (data not shown), these parameters were analyzed in all patients, *i.e.*, diabetic and non-diabetic HD patients. Multiple regression analysis was applied to identify the parameter having the strongest relationship with HOMA-IR or CRP. HOMA-IR was positively correlated with BMI ($r=0.59$, $p<0.0001$), VFA ($r=0.48$, $p<0.0001$), SFA ($r=0.66$, $p<0.0001$), triglyceride (TG) ($r=0.30$, $p<0.01$), RLP-cholesterol ($r=0.28$, $p<0.01$) and CRP ($r=0.30$, $p<0.01$) in simple regression analysis (Table 3). In multiple stepwise regression analysis, RLP-cholesterol and SFA were predominant determinants of HOMA-IR in the HD patients (Table 4). CRP was positively correlated with BMI ($r=0.23$, $p<0.05$), VFA ($r=0.43$, $p<0.0001$), SFA ($r=0.32$, $p<0.005$), TG ($r=0.31$, $p<0.01$), HDL-cholesterol ($r=0.34$, $p<0.005$), AI ($r=0.33$, $p<0.005$), immunoreactive insulin (IRI) ($r=0.28$, $p<0.01$) and HOMA-IR ($r=0.30$, $p<0.01$) in simple regression analysis (Table 3). In multiple stepwise regression analysis, VFA and HDL-cholesterol were predominant determinants of CRP in the HD patients (Table 4).

Table 3. Simple Correlation of HOMA-IR and CRP with Clinical Parameters in Hemodialysis Patients

Variables	HOMA-IR		CRP	
	r	*p*	*r*	*p*
Age	−0.14	0.24	0.21	0.07
Duration of HD	−0.22	0.06	0.01	0.48
Total cholesterol	0.08	0.51	0.003	0.98
HDL-cholesterol	−0.08	0.50	0.34	<0.005
AI	0.13	0.28	0.33	<0.005
Triglyceride	0.30	<0.01	0.31	<0.01
RLP-cholesterol	0.28	<0.01	0.15	0.18
Fasting plasma glucose	—	—	0.05	0.67
IRI	—	—	0.28	<0.01
HOMA-IR	—	—	0.30	<0.01
BMI	0.59	<0.0001	0.23	<0.05
Visceral fat area	0.48	<0.0001	0.43	<0.0001
Subcutaneous fat area	0.66	<0.0001	0.32	<0.0005
CRP	0.30	<0.01	—	—

BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; HD, hemodialysis; HDL, high-density lipoprotein; AI, atherosclerosis index; RLP, remnant-like particle; IRI, immunoreactive insulin; HOMA-IR, homeostasis model assessment–insulin resistance index; CRP, C-reactive protein.

Table 4. Stepwise Multiple Regression Analysis of Factors Associated with HOMA-IR or Serum CRP Levels in HD Patients

Variables	β value	*F* value
Dependent variables, HOMA-IR		
SFA	0.62	48.9
RLP-cholesterol	0.19	4.7
r^2	0.47	<0.0001
Dependent variables, CRP		
VFA	0.39	13.5
HDL-cholesterol	−0.26	6.2
r^2	0.25	<0.0001

F value >4.0 was considered significant. β: standard regression coefficient. r^2: coefficient of determination. HOMA-IR, homeostasis model assessment–insulin resistance index; CRP, C-reactive protein; HD, hemodialysis; SFA, subcutaneous fat area; RLP, remnant-like particle; VFA, visceral fat area; HDL, high-density lipoprotein.

Discussion

In contrast to the relation in the general population, numerous papers have stated that adiposity has a neutral or even protective association with mortality in HD patients (*11–14*). However, a number of concerns raise the possibility that the protective link observed between obesity and mortality may not actually exist. Most of the studies have not completely accounted for known mortality risk factors such as smoking, blood pressure, and medication. None of the studies have directly measured fat mass. Recently, it has become possible to directly measure both VFA and SFA with CT. However, there have been few reports on the relationship between insulin resistance or CRP and abdominal fat area measured directly with CT (*1*, *15*). In the present study, we could not determine whether adiposity has a positive or negative impact on mortality in HD patients. However, this study revealed that insulin resistance and CRP seem to have a close correlation with several fat-related parameters, including BMI, VFA and SFA. Furthermore, HOMA-IR was independently associated with SFA, but not with VFA. On the other hand, CRP was independently associated with VFA but not with SFA in HD patients.

The contribution of regional adiposity to insulin resistance in patients with type 2 DM and healthy individuals is a point of controversy. Some reports have demonstrated that both VFA and SFA independently contribute to insulin resistance in Japanese type 2 diabetics (*16*, *17*). Abate *et al*. (*18*) demonstrated that only SFA was associated with insulin resistance in non-Hispanic whites with type 2 diabetics. In contrast, VFA was predominantly related to insulin resistance in type 2 diabetics from various populations including black, white and Asian Indian populations (*8*, *9*, *19*). In HD patients, little is known about the association between abdominal fat area (AFA) and IRI. Yamauchi *et al*. (*20*) reported that VFA, but not SFA, was related to IRI in HD patients. As in our study, they demonstrated that VFA was well correlated with serum lipid abnormalities and hyperinsulinemia. In addition, their study revealed that VFA had a good correlation with abnormalities in CRP. In the present study, the contribution of SFA was much higher than that of VFA, although both VFA and SFA were associated with insulin resistance. There were also

some differences between our results and the report by Odamaki *et al*. (*21*). They failed to show that both VFA and SFA contribute to insulin resistance in HD patients. The reasons for these discrepancies are unknown. The ethnicity was the same in both studies, but the age was younger and the duration of HD was longer in the report by Odamaki *et al*. (*21*) than in our patients.

Increased RLP-cholesterol has been reported to be associated with CVD, diabetes and the requirement of HD (*22–24*). Furthermore, the levels of RLP-cholesterol in patients with both CVD and DM have been shown to be higher than those in patients with CVD without DM (*22*). Recently, Inoue *et al*. (*25*) reported that RLP-cholesterol and insulin resistance are associated with in-stent stenosis in patients with stable angina. In this study, both RLP-cholesterol and SFA were predominant determinants of HOMA-IR in the HD patients. Since insulin resistance is an independent predictor of cardiovascular mortality in HD patients (*26*), reducing the RLP-cholesterol level might prevent the development of CVD in HD patients.

Saijo *et al*. (*1*) reported an association between the CRP and VFA in healthy Japanese people. As in our study, they demonstrated that both VFA and SFA were associated with CRP, and the contribution of VFA was much higher than that of SFA. In HD patients, little is known about the association between abdominal fat area and CRP. The insulin resistance and CRP were related to each other in this study ($r=0.30$, $p<0.01$). Although both insulin resistance and CRP were important risk factors for CVD, these factors may be caused by different abdominal fat accumulation in HD patients.

Although most HD patients have maintained an appropriate BMI, VFA or visceral/subcutaneous fat (v/s) ratio were increased compared with control population (*1*), suggesting that we should pay attention to the progression or development of CVD. In conclusion, although the present study was performed on a limited number of patients, insulin resistance and CRP were related to fat-related parameters such as BMI, VFA, and SFA in HD patients. Furthermore, the contribution of SFA to insulin resistance was much higher than that of VFA, while the opposite relation was recognized for CRP.

References

1. Saijo Y, Kiyota N, Kawasaki Y, *et al*: Relationship between C-reactive protein and visceral adipose tissue in healthy Japanese subjects. *Diabetes Obes Metab* 2004; **6**: 249–258.
2. Nakanishi N, Shiraishi T, Wada M: Association between C-reactive protein and insulin resistance in a Japanese population: the Minoh Study. *Intern Med* 2005; **44**: 542–547.
3. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR: Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002; **347**: 1557–1565.
4. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE: Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA* 2005; **294**: 326–333.
5. Mohamed-Ali V, Goodrick S, Rawesh A, *et al*: Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, *in vivo*. *J Clin Endocrinol Metab* 1997; **82**: 4196–4200.
6. Mak RH, DeFronzo RA: Glucose and insulin metabolism in uremia. *Nephron* 1992; **61**: 377–382.
7. Kobayashi S, Maejima S, Ikeda T, Nagase M: Impact of dialysis therapy on insulin resistance in end-stage renal disease: comparison of haemodialysis and continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant* 2000; **15**: 65–70.
8. Gautier JF, Mourier A, de Kerviler E, *et al*: Evaluation of abdominal fat distribution in noninsulin-dependent diabetes mellitus: relationship to insulin resistance. *J Clin Endocrinol Metab* 1998; **83**: 1306–1311.
9. Banerji MA, Faridi N, Atluri R, Chaiken RL, Lebovitz HE: Body composition, visceral fat, leptin, and insulin resistance in Asian Indian men. *J Clin Endocrinol Metab* 1999; **84**: 137–144.
10. Shoji T, Emoto M, Nishizawa Y: HOMA index to assess insulin resistance in renal failure patients. *Nephron* 2001; **89**: 348–349.
11. Degoulet P, Legrain M, Reach I, *et al*: Mortality risk factors in patients treated by chronic hemodialysis. Report of the Diaphane collaborative study. *Nephron* 1982; **31**: 103–110.
12. Fleischmann E, Teal N, Dudley J, May W, Bower JD, Salahudeen AK: Influence of excess weight on mortality and hospital stay in 1346 hemodialysis patients. *Kidney Int* 1999; **55**: 1560–1567.
13. Kopple JD, Zhu X, Lew NL, Lowrie EG: Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. *Kidney Int* 1999; **56**: 1136–1148.
14. Combe C, Chauveau P, Laville M, *et al*, French Study Group Nutrition in Dialysis: Influence of nutritional factors and hemodialysis adequacy on the survival of 1,610 French patients. *Am J Kidney Dis* 2001; **37** (1 Suppl 2): S81–S88.
15. Iwasaki T, Nakajima A, Yoneda M, Terauchi Y: Relationship between the serum concentrations of C-reactive protein and parameters of adiposity and insulin resistance in patients with type 2 diabetes mellitus. *Endocr J* 2006; **53**: 345–356.
16. Yatagai T, Nagasaka S, Taniguchi A, *et al*: Hypoadiponectinemia is associated with visceral fat accumulation and insulin resistance in Japanese men with type 2 diabetes mellitus. *Metabolism* 2003; **52**: 1274–1278.
17. Taniguchi A, Nakai Y, Sakai M, *et al*: Relationship of regional adiposity to insulin resistance and serum triglyceride levels in nonobese Japanese type 2 diabetic patients. *Metabolism* 2002; **51**: 544–548.
18. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Adams-Huet B, Grundy SM: Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM. *Diabetes* 1996; **45**: 1684–1693.
19. Kelley DE, Williams KV, Price JC, McKolanis TM, Goodpaster BH, Thaete FL: Plasma fatty acids, adiposity, and variance of skeletal muscle insulin resistance in type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2001; **86**: 5412–5419.
20. Yamauchi T, Kuno T, Takada H, Nagura Y, Kanmatsuse K,

Takahashi S: The impact of visceral fat on multiple risk factors and carotid atherosclerosis in chronic haemodialysis patients. *Nephrol Dial Transplant* 2003; **18**: 1842–1847.
21. Odamaki M, Furuya R, Ohkawa S, *et al*: Altered abdominal fat distribution and its association with the serum lipid profile in non-diabetic haemodialysis patients. *Nephrol Dial Transplant* 1999; **14**: 2427–2432.
22. Higashi K, Ito T, Nakajima K, *et al*: Remnant-like particles cholesterol is higher in diabetic patients with coronary artery disease. *Metabolism* 2001; **50**: 1462–1465.
23. Takase H, Shoji K, Hase T, *et al*: Effect of diacylglycerol on postprandial lipid metabolism in non-diabetic subjects with and without insulin resistance. *Atherosclerosis* 2005; **180**: 197–204.
24. Hirany S, O'Byrne D, Devaraj S, *et al*: Remnant-like particle-cholesterol concentrations in patients with type 2 diabetes mellitus and end-stage renal disease. *Clin Chem* 2000; **46**: 667–672.
25. Inoue T, Inagaki H, Hashimoto S, *et al*: Remnant-like lipoprotein particle level and insulin resistance are associated with in-stent restenosis in patients with stable angina. *Coron Artery Dis* 2007; **18**: 319–322.
26. Shinohara K, Shoji T, Emoto M, *et al*: Insulin resistance as an independent predictor of cardiovascular mortality in patients with end-stage renal disease. *J Am Soc Nephrol* 2002; **13**: 1894–1900.