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ScienceDirect
Metabolism Clinical and Experimental 60 (2011) 121 – 126
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Insulin resistance and lower plasma adiponectin increase malignancy risk in nondiabetic continuous ambulatory peritoneal dialysis patients

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Received 2 October 2009; accepted 8 February 2010

Abstract

End-stage renal disease patients have a higher risk for developing cancer. Although several causes for this increased risk have been proposed, the risk factors for cancer development in this population have not been elucidated. The aim of this study was to determine whether metabolic derangements, including insulin resistance and altered adipokines, increase the risk of developing malignancies in peritoneal dialysis (PD) patients, who are vulnerable to metabolic disorders because of excessive glucose absorbed from the dialysate. Study subjects comprised 106 nondiabetic PD patients who had been on PD for a minimum of 3 months with no overt malignancy. Baseline anthropometry, fasting glucose, insulin, and adiponectin were measured. The development of malignancy was evaluated during the follow-up period. During the mean follow-up of 47.0 ± 23.7 months, malignancy occurred in 15 patients (14.2%). The most common site of cancer was the kidney (26.7%), followed by thyroid (13.3%) and stomach (13.3%). Baseline insulin levels and homeostasis model assessment of insulin resistance were significantly higher, whereas plasma adiponectin levels were significantly lower, in patients who developed malignancy. Cox proportional hazards analysis revealed that insulin levels, homeostasis model assessment of insulin resistance, and lower adiponectin were independent predictors of malignancy. These findings demonstrate that insulin resistance and lower adiponectin levels could be risk factors for malignancy in nondiabetic PD patients.

1. Introduction

Previous studies have shown that the frequency of malignancy is higher in patients with end-stage renal disease (ESRD) than in the general population [1,2]. In a study including dialysis patients of the United States, Europe, Australia, and New Zealand, the risk of malignancy was 3.68 times higher compared with the general population [3].

Patients maintained on dialysis are suspected to be at an increased risk of malignancy for several reasons, including the presence of chronic infection, a weakened immune system, and nutritional deficiencies [4]. In addition, the persistent metabolic derangements found in dialysis patients have been proposed to alter DNA repair [5]. However, although several speculations have been made on this subject, the potential risk factors for malignancy have not previously been investigated in this particular population.

Recently, impaired lipid and glucose metabolism has been shown to be risk factors for malignancy in the general population [6]. Insulin resistance, inflammatory cytokines, and certain adipokines are proposed as possible factors involved in this process [7,8].

Uremic conditions have been proven to cause insulin resistance that is already present with a minimal decrease in glomerular filtration rate (GFR) [9,10]. Furthermore, insulin resistance is suggested to be more prevalent in patients on peritoneal dialysis (PD) in particular because of the excessive glucose load from the dialysate [11].

Therefore, we hypothesized that metabolic derangements, including insulin resistance and altered adipokines, increase the risk of developing malignancies in PD patients. We tested this hypothesis in a nondiabetic PD population with no overt malignancy, prospectively tracing the patients until the development of cancerous events.

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doi:10.1016/j.metabol.2010.02.006

2. Subjects and methods

2.1. Patient population

This is a prospective observational study of 106 ESRD patients undergoing PD. The subjects were recruited voluntarily out of 508 prevalent PD patients from a single Korean dialysis center and were followed up at Yonsei University Health System in Seoul, Korea. The patients underwent monthly chest x-ray examinations, annual fecal occult blood tests, and biannual abdominal ultrasonogram for cancer screening throughout the study period. Those who had maintained PD for longer than 3 months, who had been screened negative for malignancy, and who were without a previous history of malignancy were recruited. We excluded patients who were younger than 18 years, who had overt infections during the last 3 months before recruitment, or who had a chronic inflammatory disease such as rheumatoid arthritis or systemic lupus erythematosus. *Diabetic patients*, defined as those with a previous history of diabetes or diagnosed with diabetes by the American Diabetes Association criteria [12], were also excluded to reduce confounding factors of glucose and lipid metabolism.

Demographic data were obtained by an interview with a senior nursing clinician. Body mass index (BMI) was calculated as weight divided by height squared. To simulate the actual dialysis condition, all patients had a full abdomen at the time of sampling. Blood samples for laboratory measurements were drawn from the antecubital vein at the first 2 hours of PD exchange with 1.5% dextrose dialysate in an overnight fasting state. The preceding overnight dwell was regulated to 1.5% dextrose dialysate to standardize the glucose load. Informed consent was obtained from all participants before study entry.

2.2. Laboratory measurements

Plasma was separated from blood within 30 minutes and stored at −70°C until analysis. Fasting blood glucose was determined by the glucose oxidase method. Serum total cholesterol, high-density lipoprotein cholesterol, and triglyceride (TG) concentrations were measured by an autoanalyzer using an enzymatic colorimetric method (Hitachi 7150; Hitachi, Tokyo, Japan). Low-density lipoprotein cholesterol was calculated using the Friedewald formula. High-sensitivity C-reactive protein (hsCRP) levels were determined using a BN II analyzer (Dade Behring, Newark, DE) by a latex-enhanced immunonephelometric method. Plasma adiponectin (B-Bridge International, Sunnyvale, CA) levels were measured by an enzyme-linked immunosorbent assay.

2.3. Estimation of insulin resistance

Insulin resistance was calculated by the homeostasis model assessment (HOMA-IR) using the following formula:

$$\text{HOMA}-\text{IR} = [\text{fasting insulin (in microunits per milliliter)} \times \text{fasting serum glucose (in millimoles per liter)} / 22.5]$$

2.4. Follow-up and end points

Patients were prospectively followed up from January 2004 until the diagnosis of malignancy, death, a switch to an alternative dialysis modality, or December 2009. One patient was lost during the follow-up period, and the data were excluded from the analysis. The date of diagnosis of malignancy was defined as the end point. Mortality due to causes other than malignancy and patients who switched to hemodialysis or transplantation were treated as censored for cancer-free survival analysis.

2.5. Statistical analysis

Statistical analyses were performed using SPSS software for Windows, version 13.0 (SPSS, Chicago, IL). All data are expressed as mean ± SD unless otherwise specified. Because of the log-normally distributed values of insulin, HOMA-IR, hsCRP, and TG, their natural log values were used for analysis. Geometric means for all log-normally distributed continuous variables were calculated and are reported with 95% confidence intervals (CIs), whereas the duration of PD is reported with median values and ranges. To compare differences between patients who developed cancer and those who did not, Student t test or the Mann-Whitney U test was used for continuous variables; and the χ^2 test was used for categorical variables. To assess cross-sectional interrelationships between metabolic and inflammatory variables, Spearman partial correlation coefficients, adjusted for age and sex, were used for analyzing data from patients who did not develop malignancy. Cox proportional hazards analysis was performed to determine risk factors for cancer development. P values < .05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

Baseline patient characteristics are shown in Table 1. The mean age was 51.6 ± 13.2 years, 49 patients (46.2%) were male, and the mean insulin level was 7.5 μU/mL (95% CI, 6.6-8.6 μU/mL). The median PD duration was 83.4 months (range, 6.7-210.6 months). All patients were prescribed for continuous ambulatory PD.

Table 1
Baseline characteristics of the study population

Age (y)	51.6 ± 13.2
Sex (male)	49 (46.2%)
Duration of PD (mo)	83.4 (6.7-210.6)
Primary kidney disease	
Hypertension	24 (22.6%)
Glomerulonephritis	27 (25.5%)
Others	13 (12.3%)
Unknown	42 (39.6%)

Data are expressed as mean ± SD, except for the duration of PD that is expressed as the median value (range).

3.2. Clinical outcomes during the follow-up period

During the 47.0 ± 23.7–month follow-up period, 15 patients were diagnosed with malignancy. Malignancy of the urogenital origin was the most common type diagnosed: kidney (4 cases), ureter (1 case), and bladder (1 case), followed by the thyroid (2 cases), stomach (2 cases), lung (1 case), breast (1 case), cervix (1 case), ovary (1 case), and liver (1 case). When the number of newly diagnosed malignancies was analyzed for each of the 6-year follow-up period from 2004 to 2009, 1 case of malignancy was found in the year 2004, 3 cases in 2005, 4 cases in 2006, 2 cases in 2007, 3 cases in 2008, and 2 cases in 2009.

3.3. Comparison between patients with and without cancer

When comparisons were made between patients who developed cancer and those who did not, patients with cancer had higher baseline insulin levels (11.9 [95% CI, 8.0-17.7] vs 6.8 μU/mL [95% CI, 6.0-8.0], P = .005), HOMA-IR (2.8 [95% CI, 1.8-4.2] vs 1.5 [95% CI, 1.3-1.8], P = .008), white blood cell (WBC) counts (7527.3 ± 1528.7 vs 6210.9 ± 1649.8/μL, P = .005), and hsCRP levels (2.36 [95% CI, 1.21-4.58] vs 0.94 mg/dL [95% CI, 0.73-1.24], P = .01), whereas plasma adiponectin levels (17.2 ± 7.9 vs 22.3 ± 8.0 ng/mL, P = .02) were significantly lower. When analysis was done on WBC differential counts, absolute neutrophil counts (4817.4 ± 1427.0 vs 4021.6 ± 1308.3/μL, P = .03) and lymphocyte counts (1777.5 ± 483.9 vs 1423.6 ± 572.9/μL, P = .03) were significantly higher in patients with malignancy. In contrast, there were no differences in fasting glucose (94.9 ± 11.7 vs 92.9 ± 16.7 mg/dL, P = .65) between those who developed malignancy and those who did not (Table 2).

Table 2
Comparison between patients with and without malignancy

	Without malignancy (n = 91)	With malignancy (n = 15)	P
Age (y)	51.3 ± 9.9	53.1 ± 9.6	.51
Sex (male)	45 (49.5%)	4 (26.7%)	.16
BMI (kg/m^2)	23.9 ± 2.9	25.5 ± 3.7	.08
Duration of PD (mo)	77.1 (6.7-210.6)	103.5 (52.4-200.5)	.05
Smoking history (%)	31 (34.1)	3 (20.0)	.38
Fasting glucose (mg/dL)	92.9 ± 16.7	94.9 ± 11.7	.65
Insulin (μU/mL)	6.8 (6.0-8.0)	11.9 (8.0-17.7)	.005
HOMA-IR	1.5 (1.3-1.8)	2.8 (1.8-4.2)	.008
WBC count (/μL)	6210.9 ± 1649.8	7527.3 ± 1528.7	.005
ANC (/μL)	4021.6 ± 1308.3	4817.4 ± 1427.0	.03
ALC (/μL)	1423.6 ± 572.9	1777.5 ± 483.9	.03
AMC (/μL)	338.2 ± 181.2	417.8 ± 142.3	.11
AEC (/μL)	345.1 ± 308.9	392.4 ± 212.0	.57
ABC (/μL)	35.9 ± 22.0	38.3 ± 21.3	.70
hsCRP (mg/dL)	0.94 (0.73-1.24)	2.36 (1.21-4.58)	.01
Total cholesterol (mg/dL)	191.2 ± 39.1	189.3 ± 30.8	.86
TG (mg/dL)	127.8 (113.5-145.5)	158.5 (115.5-217.4)	.19
HDL (mg/dL)	45.5 ± 13.1	39.7 ± 8.3	.11
LDL (mg/dL)	113.0 ± 35.0	112.4 ± 40.2	.95
Adiponectin (ng/mL)	22.3 ± 8.0	17.2 ± 7.9	.02

Data are expressed as mean ± SD or geometric mean (95% CI), except for the duration of PD that is expressed as the median value (range). ANC indicates absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; AEC, absolute eosinophil count; ABC, absolute basophil count; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

3.4. Associations between metabolic factors and inflammatory markers

Correlations between metabolic factors, BMI, WBC counts, and hsCRP levels adjusted for age and sex were estimated using Spearman correlation coefficients in patients without malignancy. White blood cell count was positively correlated with BMI (r = 0.26, P = .01), insulin levels (r = 0.34, P = .005), and HOMA-IR (r = 0.35, P = .005). However, fasting glucose levels (r = 0.17, P = .10) did not show significant correlations with WBC. High-sensitivity CRP showed positive correlations with BMI (r = 0.33, P = .006), insulin levels (r = 0.24, P = .02), and HOMA-IR (r = 0.24, P = .02), whereas there were no significant correlations with fasting glucose levels (r = 0.12, P = .23). Plasma adiponectin levels were negatively correlated with WBC (r = −0.47, P < .001) and hsCRP levels (r = −0.38, P < .001).

3.5. Predictors of malignancy

Results of univariate and multivariate Cox proportional hazards analysis models on metabolic factors and inflammatory markers are displayed in Table 3. Univariate Cox regression analysis revealed that higher insulin levels (relative risk [RR], 1.05 [95% CI, 1.01-1.08]; P = .01), HOMA-IR (RR, 1.16 [95% CI, 1.01-1.34]; P = .03), WBC counts (RR, 1.62 [95% CI, 1.17-2.26]; P = .004), and hsCRP levels (RR, 1.02 [95% CI, 1.01-1.03]; P = .01), and lower adiponectin (RR, 0.94 [95% CI, 0.89-0.99]; P = .03) were significant factors for malignancy development. However, age (RR, 1.01 [95% CI, 0.96-1.06]; P = .72), sex (RR, 0.39 [95% CI, 0.13-1.21]; P = .10), BMI (RR, 1.16 [95% CI, 0.99-1.37]; P = .07), dialysis duration (RR, 1.01 [95% CI, 0.99-1.02]; P = .16), smoking history (RR, 0.52 [95% CI, 0.15-1.81]; P = .30), and fasting glucose levels (RR, 1.01 [95% CI, 0.97-1.04]; P = .77) were not significantly related to the development of malignancy. Further adjustments made in successive models revealed that higher insulin, HOMA-IR, and WBC counts, and lower adiponectin levels remained robust as significant predictors of malignancy in all models. Insulin levels (RR, 1.05 [95% CI, 1.01-1.13]; P = .03), HOMA-IR (RR, 1.22 [95% CI, 1.01-1.50]; P = .03), WBC counts (RR, 1.43 [95% CI, 1.03-1.99]; P = .03), and lower adiponectin (RR, 0.94 [95% CI, 0.88-0.99]; P = .04) were independent predictors of malignancy when adjustments were made for age, sex, dialysis duration, smoking, and BMI.

Table 3
Hazard ratios and 95% CIs for malignancy risk according to metabolic factors and inflammatory markers

	RR[a] (95% CI)	RR[b] (95% CI)	RR[c] (95% CI)	RR[d] (95% CI)
	P	*P*	*P*	*P*
Insulin (μU/mL)	1.05 (1.01-1.08)	1.06 (1.02-1.10)	1.06 (1.01-1.10)	1.05 (1.01-1.13)
	.01	.01	.01	.03
HOMA-IR	1.16 (1.01-1.34)	1.23 (1.04-1.45)	1.23 (1.03-1.47)	1.22 (1.01-1.50)
	.03	.02	.02	.03
WBC ($10^3/\mu$L)	1.62 (1.17-2.26)	1.54 (1.11-2.14)	1.54 (1.12-2.12)	1.43 (1.03-1.99)
	.004	.01	.01	.03
hsCRP (10^{-1} mg/dL)	1.02 (1.01-1.03)	1.01 (1.01-1.02)	1.01 (1.01-1.02)	1.01 (0.99-1.03)
	.01	.04	.04	.08
Adiponectin (ng/mL)	0.94 (0.89-0.99)	0.93 (0.88-0.99)	0.94 (0.88-0.99)	0.94 (0.88-0.99)
	.03	.02	.02	.04

[a] Model 1: unadjusted relative risk.
[b] Model 2: adjusted for age and sex.
[c] Model 3: adjusted for model 2 plus dialysis duration and smoking history.
[d] Model 4: adjusted for model 3 plus BMI.

4. Discussion

In the present study, we demonstrated that insulin resistance and lower plasma adiponectin are associated with a greater risk of malignancy in nondiabetic PD patients.

An increased incidence of malignancy has been reported in patients with chronic renal failure [2]. Recently, in a population-based cohort study of 3654 patients, the excess risk for malignancy was found to begin at an estimated GFR of 55 mL/(min 1.73 m^2) and increase linearly as GFR declined to a greatest excess risk of 3.0 times for all types of malignancies [13]. In the present study, the incidence of malignancy was approximately 12-fold higher than the age-matched national cancer incidence rate, which is a higher RR than previous reports [14]. The reason for this higher incidence of malignancy could be attributed to the much longer duration of dialysis in the present study compared with other observational reports [14]. Moreover, the fact that previous reports regarding increased risks of malignancy in ESRD patients were made based on observations of mostly hemodialysis patients should also be considered. However, although patients who developed malignancies showed a trend for having a longer dialysis duration, dialysis duration itself was not a significant predictor of malignancy. We surmise that the influence of PD duration on metabolic derangements, which are suspected to be associated with malignancy, may become weak when the PD duration surpasses a certain length of time. Nevertheless, because of the comparatively long and narrowly distributed dialysis duration of the studied patients, an analysis on a larger population should be needed to validate this time-dependent relationship.

In contrast to the elevated incidence of squamous cell carcinoma and lymphoproliferative malignancies in transplant recipients, malignancies in dialysis patients are known to be relatively common types of tumors such as cancers of the breast, kidney, lung, and thyroid [2,3]. Among them, renal cell carcinomas occur at a high incidence particularly in ESRD patients treated with dialysis [15]. Extended proliferation of proximal tubules as a compensation for nephron loss, combined with the uremic milieu and renal ischemia, is known to contribute to malignant transformation of renal cells [16,17]. In accordance with previous reports, we also found that malignancies of the kidneys were the most common cancer type. Malignancies excluding those of urogenital origin found in this population are comparable to the types found in the general population, considering that the most frequent malignancies diagnosed in Korea are cancers of the stomach, lung, colon, liver, thyroid, and breast, in order [14].

Previously, factors related to uremia itself or transplantation-associated immunosuppressants have been assumed to increase the incidence of malignancy in ESRD patients [4]. In the general population, however, metabolic derangements have recently been proposed as causes of malignancies [18]. Various studies have shown that insulin resistance increases the risk of cancers of the pancreas, endothelium, colon, liver, and kidney in diabetic patients [19-23]. Although the molecular mechanisms underlying this finding are still a subject of ongoing research, cell proliferation activated by signaling pathways downstream of the insulin and insulin-like growth factor–1 receptors has been proposed as an answer [24]. Glucose metabolism is altered in chronic kidney disease patients even in early stages, and the most common manifestation is insulin resistance [25]. In PD patients in particular, exposure to high–glucose concentration solutions during PD intensifies this metabolic abnormality [26]. In the present study, insulin resistance was an independent risk factor for malignancy. The observations of the present study support the notion that metabolic derangements aggravated by reduced renal function and even by PD itself could increase the risk of malignancy in nondiabetic PD patients.

Adiponectin, an adipocytokine whose levels decrease in obesity and insulin resistance, has also been found to have a close association with the development and progression of several malignancies in the general population [27-30].

Adiponectin's association with malignancy could be due to its well-characterized effects on insulin resistance, but direct effects such as the decrease in the antiproliferative actions of adiponectin have also been proposed to play a role [31]. Adiponectin levels are known to be elevated in ESRD patients [32]. However, despite this modest ESRD-associated hyperadiponectinemia, lower adiponectin levels have still been shown to be risk factors for cardiovascular disease in dialysis patients. These findings support the hypothesis that the relationship between adiponectin levels and disease in ESRD may be reset at a higher level [33]. Moreover, high glucose PD fluids have been shown to reduce adiponectin production in adipocytes [34]; and changes to nonglucose PD solutions have been proven to increase adiponectin levels in humans [35]. The relationship between adiponectin levels and malignancy risk in this study suggests that lower adiponectin levels could increase the risks of developing malignancies in nondiabetic PD patients.

Both hsCRP levels and peripheral WBC counts were found to be significant predictors of malignancy in the present study. Chronic inflammation has previously been proposed to be a risk factor for malignancy, and an association between WBC counts and malignancy in the general population has recently been demonstrated [36]. Inflammatory markers were closely related to insulin resistance and adiponectin levels in this study, which is in concordance with previous reports that have shown that these metabolic disturbances are proinflammatory [37,38]. These findings suggest that metabolic abnormalities and inflammation are interrelated and do not impose separate risks for malignancy. Previously, it has been suggested that viral infection may be a cause of the increased cancer risk in ESRD patients [3]. However, the predominance of the number of neutrophils as well as lymphocytes in patients with malignancies suggests that DNA damage due to neutrophils, resulting from metabolic causes and the chronic kidney disease condition itself, could also explain this increased risk [39].

There are a number of limitations to this study. Because this is a relatively small-sized study of a single center, further larger-scaled studies are needed to confirm the findings. In addition, the collection of dialysis specific variables was limited. Although most of the patients in this study are thought to be anuric because of the comparatively long dialysis duration, data on residual renal function should also be considered in future investigations.

In conclusion, the incidence of malignancy is increased in nondiabetic PD patients according to the present findings. Although further research should be conducted to confirm the cancer-preventative effects of improving insulin resistance, the results of this study suggest that metabolic derangements, including insulin resistance and lower adiponectin levels as well as chronic inflammation, could contribute to the increased risk of malignancy in nondiabetic patients undergoing PD with glucose-containing solutions [40].

Acknowledgment

This work was supported by a grant of the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare, and Family Affairs, Republic of Korea (A084001).

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