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Original Article

Insulin resistance is associated with new-onset cardiovascular events in nondiabetic patients undergoing peritoneal dialysis



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ABSTRACT

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Background: Chronic exposure to high glucose-containing peritoneal dialysis solution and consequent abdominal obesity are potential sources of insulin resistance in patients requiring prevalent peritoneal dialysis. The aim of this study was to elucidate the prognostic values of insulin resistance on new-onset cardiovascular events in nondiabetic patients undergoing prevalent peritoneal dialysis.

Methods: A total of 201 nondiabetic patients undergoing prevalent peritoneal dialysis were recruited. Insulin resistance was assessed by homeostatic model assessment of insulin resistance (HOMA-IR). The primary outcome was new-onset cardiovascular events during the follow-up period. Cox proportional hazard analysis was performed to ascertain the independent prognostic value of HOMA-IR for the primary outcome.

Results: The mean age was 53.1 years and male was 49.3% ($n=99$). The mean HOMA-IR was 2.6 ± 2.1 . In multivariate linear regression, body mass index ($\beta=0.169$, $P=0.011$), triglyceride level ($\beta=0.331$, $P<0.001$), and previous cardiovascular diseases ($\beta=0.137$, $P=0.029$) were still significantly associated with HOMA-IR. During a mean follow-up duration of 36.8 ± 16.2 months, the primary outcome was observed in 36 patients (17.9%). When patients were divided into tertiles according to HOMA-IR, the highest tertile group showed a significantly higher incidence rate for new-onset cardiovascular events compared to the lower two tertile groups ($P=0.029$). Furthermore, multivariate Cox analysis revealed that HOMA-IR was an independent predictor of the primary outcome (hazard ratio=1.18, 95% confidence interval=1.03–1.35, $P=0.014$).

Conclusion: Insulin resistance measured by HOMA-IR was an independent risk factor for new-onset cardiovascular events in nondiabetic patients undergoing prevalent peritoneal dialysis.

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Introduction

Cardiovascular disease (CVD) is the most important and leading cause of death in those with end-stage renal disease (ESRD) [1,2]. In the general population, insulin resistance is related to several risk factors for CVD, including hypertension,

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dyslipidemia, diabetes, and central obesity [3]. Furthermore, hyperinsulinemia itself and related-insulin resistance are directly associated with development of CVD [4,5].

In patients with ESRD, many factors including uremia, chronic inflammation, and abnormal adipokines are involved in the development of insulin resistance. Previous studies revealed that insulin resistance was prevalent and was an independent predictor of cardiovascular mortality in nondiabetic patients with ESRD and on hemodialysis (HD) [6]. In particular, in patients on peritoneal dialysis (PD), chronic exposure to high glucose-containing PD solution causes several hazard events including hypertriglyceridemia, poor glycemic control, new-onset diabetes, and central obesity [7]. It is likely that these abnormalities aggravate insulin resistance in patients on PD [7]. Furthermore, a recent study also showed a relationship between insulin resistance, as assessed by homeostatic model assessment of insulin resistance (HOMA-IR), and CVD in patients on PD [8–10]. However, due to the relatively small sample size and the very low incidence rate of CVD seen in a previous study, earlier results would benefit from validation of the predictive role of insulin resistance in a larger population. Therefore, we investigated whether insulin resistance determined by HOMA-IR was an independent predictor of cardiovascular outcome in nondiabetic patients with ESRD and on PD.

Methods

Ethics statement

The study was carried out in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Yonsei University Health System (YUHS) Clinical Trial Center, Seoul, Korea. We obtained informed written consent from all participants involved in the current study.

Patients

All consecutive nondiabetic patients with ESRD older than 18 years of age who underwent PD for > 3 months at YUHS were initially screened for enrollment between January 2009 and December 2009 in this prospective observational study. Patients were considered eligible if they had no history of malignancy or chronic inflammatory disease such as systemic lupus erythematosus or rheumatoid arthritis, and had no overt infection during the 3 months prior to study entry. We also excluded patients with a history of kidney transplantation, a history of HD for > 3 months prior to PD, or a history of CVD within 3 months prior to study entry (Fig. 1).

Clinical and biochemical data collection

Demographic and clinical data recorded at study entry included: age, sex, PD duration, primary renal disease, smoking status, and medication use. Body mass index (BMI) and biochemical data were measured at study enrollment. Patients were weighed in light clothing, and height was measured with shoes off. BMI was calculated as weight/height (kg/m^2). Diabetes mellitus was defined as previously described [11]. Blood was taken after a 12-hour overnight fast, and the following laboratory data were measured: hemoglobin, glucose, blood urea nitrogen, creatinine, albumin, iron profile, triglyceride (TG), total

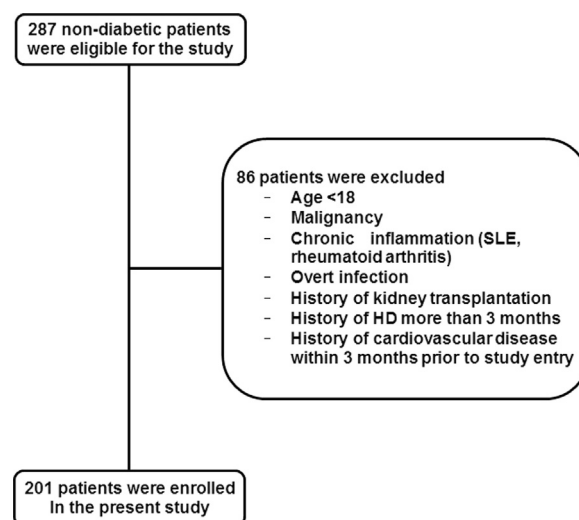


Figure 1. A flow diagram of the study. All patients with ESRD older than 18 years of age who underwent PD for > 3 months were initially screened for enrollment between January 2009 and December 2009. Excluding 86 patients, a total of 201 patients were enrolled. HD, hemodialysis; SLE, systemic lupus erythematosus.

cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), calcium, phosphorus, and intact parathyroid hormone (iPTH) concentrations. Insulin resistance was assessed using the HOMA-IR equation as follows:

$$\text{HOMA-IR} = \left(\frac{\text{fasting insulin in microunits per liter}}{\text{fasting plasma glucose in mmol/L} / 22.5} \right) \quad (1)$$

In addition, high-sensitivity C-reactive protein (hs-CRP) concentrations were determined by a latex-enhanced immunonephelometric method using a BNII analyzer (Dade Behring, Newark, DE, USA). Kt/V urea was determined from the total loss of urea nitrogen in spent dialysate using PD Adequest 2.0 for Windows software (Baxter Healthcare, Deerfield, IL, USA).

Follow-up and end points

Patients were followed up at 3-month intervals through January 1, 2014. All deaths and hospitalizations were noted in a serious adverse event database. All events were retrieved from the database and carefully reviewed to determine incident CVD. Primary outcomes were major cardiovascular events, which were defined as death or hospitalization from an acute coronary syndrome and stable angina requiring coronary revascularization or coronary artery bypass surgery. Cerebrovascular events were defined as transient ischemic attack, stroke, or carotid endarterectomy and peripheral vascular disease defined as ischemic limb loss and/or ulceration or peripheral revascularization procedure that also included major cardiovascular events. When a patient died within 60 days after transfer to HD, the death was regarded as a mortality event. Loss to follow-up, kidney transplantation, and transfer to HD were censored in the final analysis.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation, or median (interquartile range), whereas categorical variables were expressed as a number (percentage). Normality of distribution was ascertained by the Kolmogorov-Smirnov test.

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