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Irisin, a novel myokine is an independent predictor for sarcopenia and carotid atherosclerosis in dialysis patients

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ABSTRACTS

Objective: In end-stage renal disease, deleterious effect of sarcopenia on cardiovascular disease has been explained mainly by chronic inflammation. However, evidence emerged that skeletal muscles mediate their protective effect against sarcopenia by secreting myokines. Therefore, we sought to investigate the effect of irisin, a recently introduced myokine, on the association between sarcopenia and cardiovascular disease in peritoneal dialysis (PD) patients.

Methods: Serum irisin concentrations were assessed by enzyme-linked immunosorbent assay in 102 prevalent PD patients and 35 age- and sex-matched controls. To determine sarcopenia and cardiovascular disease, anthropometric indices including mid-arm muscle circumference (MAMC) and carotid intima-media thickness (cIMT) were measured.

Results: Serum irisin concentrations were significantly lower in PD patients than in controls (184.2 ± 88.0 vs. 457.2 ± 105.5 ng/mL, $P < 0.001$). In PD patients, univariate linear regression analysis showed that serum irisin was positively correlated with MAMC and thigh circumference, but negatively correlated with residual renal function and cIMT. Multivariate analysis revealed that MAMC (per 1 cm increase, $B = 8.78$, 95% confidence interval [CI] = 0.77–16.79, $P = 0.03$) had an independent association with serum irisin. In addition, serum irisin was a significant independent predictor for carotid atherosclerosis even after adjustment for high-sensitivity C-reactive protein in PD patients (per 1 g/mL increase, odds ratio = 0.990, 95% CI = 0.982–0.997, $P = 0.007$).

Conclusion: This study demonstrated that serum irisin was significantly associated with sarcopenia and carotid atherosclerosis in PD patients. Additional studies to provide a confirmation and examine possible mechanisms are warranted.

1. Introduction

Cardiovascular disease is the leading cause of death in end-stage renal disease (ESRD) patients [1]. Protein-energy wasting (PEW) is regarded as an important nontraditional risk factor for development of cardiovascular disease in this population [2]. Sarcopenia, reduction in muscle mass, is frequently observed in PEW and is prevalent in chronic kidney disease (CKD) patients [3,4]. In ESRD patients, sarcopenia is significantly associated with greater mortality [4]. Several possible explanations have been proposed for the protective effect of muscle against sarcopenia in ESRD such as association with chronic inflammation [5], nutritional status [6], uremia [2], or insulin resistance [7]. In addition to these factors, skeletal muscles are suggested to mediate their protective effects via secretion of proteins that exert specific endocrine effects [8]. Indeed, skeletal muscles produce and release cytokines or other

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peptides that are classified as myokines [9]. Myokines have been known to stimulate muscle growth and hypertrophy, increase fat oxidation, enhance insulin sensitivity, and induce anti-inflammatory activity [8]. Irisin, a novel myokine, has been introduced to drive brown-fat-like conversion of white adipose tissue and stimulate thermogenic genes including uncoupling protein 1 (UCP1) [10]. In mouse models, increased plasma irisin reduced weight gain, glucose intolerance, and insulin resistance under a high-fat diet [10]. Although the exact characteristics of irisin are controversial [11,12], irisin is proposed to be linked, at least in part, to the beneficial effects of skeletal muscle on energy homeostasis and glucose metabolism [10,11].

To date, few studies have investigated irisin in CKD patients [13–15]. Previous studies in CKD patients indicated that irisin concentrations were significantly lower in CKD patients than in control patients [13–15]. Since irisin is secreted from myocytes, it can be speculated that sarcopenia would lead to a decrease in irisin. Therefore, we primarily investigated the association between irisin and sarcopenia. In addition, sarcopenia was an independent risk factor for cardiovascular morbidity and mortality [3,4]. In this regard, we hypothesized that irisin had significant association with sarcopenia and cardiovascular disease. To address these issues, we determined serum irisin concentrations, cardiometabolic risk factors, anthropometric indices, and carotid atherosclerosis by ultrasonography in 102 peritoneal dialysis (PD) patients and 35 healthy controls. To the best of our knowledge, this is the first study to explore the pathophysiologic role of irisin on cardiovascular disease in patients with renal insufficiency.

2. Methods

2.1. Subjects

The study population for this study is comprised of participants in a prospective cohort, which included prevalent PD patients in Yonsei University Health System (YUHS), designed to investigate the effect of body composition on cardiovascular risk and mortality in PD patients. In our previous report [16], we included 88 prevalent PD patients between February 2010 and July 2010. Due to limitation of relatively small subject numbers, we maintained and extended this cohort. We excluded patients who were <20 years of age or >80 years and those who were on PD for less than 3 months. Patients were eligible if they had no history of malignancy or chronic inflammatory disease such as systemic lupus erythematosus, and had no overt infection or cardiovascular hospitalization during the 3 months prior to study enrollment. Patients were excluded if they had a history of kidney transplantation or hemodialysis (HD) prior to PD. A total of 102 prevalent PD patients were finally analyzed (Supplementary Figure 1). Thirty-five age- and gender-matched healthy controls were selected from the Cardiovascular Genome Center Registry from YUHS. This study was carried out in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the YUHS Clinical Trial Center. We obtained informed written consent from all participants.

2.2. Clinical and biochemical data collection

Demographic and clinical data collected at study enrollment were: age, gender, diabetes mellitus, previous history of cardiovascular disease, smoking status, physical activity, and medication. Cardiovascular disease was defined as a history of coronary, cerebrovascular, or peripheral vascular disease. Coronary artery disease was defined as a history of angioplasty, coronary artery bypass graft, myocardial infarction or angina. Cerebrovascular disease was defined as previous transient ischemic attack, stroke, or carotid endarterectomy. Peripheral vascular disease was defined as a history of claudication, ischemic limb loss and/or ulceration, or performance of a peripheral revascularization procedure. Blood was taken after a 12-h overnight fast, and the following laboratory data were measured in our hospital laboratory at the time of study enrollment: hemoglobin, glucose, blood urea nitrogen, creatinine, albumin, triglyceride, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, calcium (Ca), phosphorus (P), and intact parathyroid hormone concentrations. 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). Residual renal function (RRF) was calculated as the average clearance of urea and creatinine from 24-h urine collection in PD patients. In controls, estimated glomerular filtration rate (eGFR) was calculated by the four-variable Modification of Diet in Renal Disease Study formula. To reflect actual patient conditions, usual overnight peritoneal dialysate volume and glucose concentrations were not changed for this study. 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).

2.3. Measurement of serum irisin and plasma interleukin-6

At study enrollment, 10 mL of whole blood was taken using serum separation tube (SST) and ethylenediaminetetraacetic acid (EDTA) tube. The aliquots of serum and plasma were stored at a deep freezer (−70 °C). Serum irisin concentrations were measured from stored serum samples by colorimetric enzyme-linked immunosorbent assay (ELISA) (AG-45A-0046EK-KI01, Adipogen, San Diego, CA, USA). Interassay and intraassay coefficients of variation were less than 15% and less than 10% for irisin. Plasma interleukin-6 (IL-6) was determined by ELISA (Human IL-6 Quantikine ELISA Kit, R&D Systems, Inc., Minneapolis, MN, USA) in 76 PD patients.

2.4. Anthropometric measurement

Anthropometric indices were measured in the morning after complete emptying of overnight dialysate at the time of study enrollment. Patients were weighed in light clothing, and height was measured with no shoes. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Triceps skinfold thickness was measured with a conventional skinfold caliper using standard techniques [17]. The mid-arm circumference and thigh circumference was measured with a plastic tape. These anthropometric measurements were obtained by a single skilled nurse in our PD unit and the mean value of the triplicate measurements was used in the analysis. Mid-arm muscle circumference (MAMC) was calculated as MAMC (cm) = mid-arm circumference (cm) − π × triceps skinfold thickness (cm) [4].

2.5. Carotid atherosclerosis assessment

Carotid intima-media thickness (cIMT) was assessed using a Prosound α10 (Aloka, Tokyo, Japan) by a single trained medical doctor who was blinded to patients' clinical and biochemical data at the time of study enrollment. The cIMT was measured in the prone position with head extended and turned to the opposite direction. Common carotid arteries, carotid bulb, and internal carotid arteries were examined by two different longitudinal projections. The cIMT was measured as the distance between the leading edges of the lumen interface and the media-adventitia interface at 10 mm