Anemia and Left Ventricular Hypertrophy With Renal Function Decline and Cardiovascular Events in Chronic Kidney Disease

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Abstract: *Background:* Anemia is a common complication in patients with chronic kidney disease (CKD), which may initiate or accelerate left ventricular hypertrophy (LVH). This study is designed to assess whether the coexistence of anemia and LVH is independently associated with the rate of renal function decline and increased cardiovascular events in patients with CKD stages 3 to 5. *Methods:* This longitudinal study enrolled 415 patients, who were classified into 4 groups according to sex-specific median values of hemoglobin and with/without LVH. The change in renal function was measured by estimated glomerular filtration rate slope. Cardiovascular events were defined as cardiovascular death, hospitalization for unstable angina, nonfatal myocardial infarction, sustained ventricular arrhythmia, hospitalization for congestive heart failure, transient ischemia attack, and stroke. The relative risk of cardiovascular events was analyzed by Cox's regression method. *Results:* The estimated glomerular filtration rate slope was significantly lower in the group with lower hemoglobin and LVH than in the other groups ($P \leq 0.031$). In addition, patients with lower hemoglobin and LVH were independently associated with increased cardiovascular events (hazard ratio, 4.269; 95% confidence interval, 1.402–13.000; $P = 0.011$). *Conclusions:* Our findings showed that the coexistence of anemia and LVH was independently associated with faster renal function decline and poor cardiovascular outcomes in patients with CKD. Assessments of serum hemoglobin level and LVH by echocardiography may help identify a high-risk group of poor renal and cardiovascular prognosis in patients with CKD stages 3 to 5.

Key Indexing Terms: Anemia; Left ventricular hypertrophy; Chronic kidney disease; Renal function decline; Cardiovascular events. **[Am J Med Sci 2014;347(3):183–189.]**

Anemia is common in chronic kidney disease (CKD) patients, which not only causes cardiovascular disease such as coronary artery disease and congestive heart failure but also accelerates the progression of renal dysfunction.[1,2] Some studies have claimed that anemia is an independent risk factor for progression to end-stage renal disease,[3,4] whereas others have failed to identify anemia as a significant and independent risk factor.[5] Thus, the status of anemia as an independent risk marker for progression of renal function decline remains controversial. Besides, the relationship between anemia and cardiovascular events also needs to be clarified.

Chronic anemia is known to result in increased cardiac output that may lead to the development of left ventricular hypertrophy (LVH).[6,7] LVH is also reported to be an independent risk factor for adverse renal and cardiovascular outcomes in CKD.[8,9]

The hypothesis that the coexistence of anemia and LVH is a risk factor for renal dysfunction progression and adverse cardiovascular outcomes has never been examined. Accordingly, the aim of this study was to assess whether the coexistence of anemia and LVH is independently associated with rate of renal function decline and increased cardiovascular events in patients with CKD stages 3 to 5.

SUBJECTS AND METHODS

Study Patients and Design

The study was conducted in a regional hospital in southern Taiwan. We consecutively enrolled 518 predialysis outpatients with stages 3 to 5 of CKD according to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines[10] from our Outpatient Department of Internal Medicine from January 2007 to May 2010. We classified our patients with evidence of kidney damage lasting for more than 3 months into CKD stages 3, 4 and 5, based on estimated glomerular filtration rate (eGFR) level ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) of 30 to 59, 15 to 29 and <15, respectively. Exclusion criteria were significant mitral valve disease in 3 patients and inadequate image visualization in 5 patients. Five patients refused echocardiography examinations because of personal reasons. Fifty-one patients with less than 3 eGFR measurements during the follow-up period were excluded. In addition, those patients with mortality (n = 9) or entering dialysis therapy (n = 30) within 3 months after enrollment were also excluded to avoid incomplete observation of change in renal function. Finally, 415 patients (mean age, 66.6 ± 12.1 years; 265 males) were included in this study. The protocol was approved by our Institutional Review Board, and all enrolled patients gave written informed consent.

Evaluation of Cardiac Structure and Function

The echocardiographic examination was performed by 2 experienced cardiologists with a VIVID 7 (General Electric Medical Systems, Horten, Norway), with the participant respiring quietly in the left decubitus position. The cardiologists were blind to the other data. Two-dimensional and 2 dimensionally guided M-mode images were recorded from the standardized views. The echocardiographic measurements included left ventricular internal diameter in diastole (LVIDd), left ventricular posterior wall thickness in diastole (LVPWTd), interventricular septal wall thickness in diastole (IVSTd), peak

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early transmitral filling wave velocity (E), peak late transmitral filling wave velocity (A), and E:A ratio. Left ventricular systolic function was assessed by left ventricular ejection fraction (LVEF). Left ventricular mass was calculated using Devereux-modified method, that is, left ventricular mass = $1.04 \times ([IVSTd + LVIDd + LVPWTd]^3 - LVIDd^3) - 13.6g$.[11] Left ventricular mass index (LVMI) was calculated by dividing left ventricular mass by body surface area. LVH was defined as suggested by the 2007 European Society of Hypertension/European Society of Cardiology guidelines.[12]

Collection of Demographic, Medical, and Laboratory Data

Demographic and medical data including age, gender, smoking history (ever versus never) and comorbid conditions were obtained from medical records or interviews with patients. The body mass index was calculated as the ratio of weight in kilograms divided by square of height in meters. Laboratory data were measured from fasting blood samples using an autoanalyzer (D-68298 Mannheim COBAS Integra 400; Roche Diagnostics GmbH, Mannheim, Germany). Serum creatinine was measured by the compensated Jaffé's (kinetic alkaline picrate) method in a Roche/Integra 400 Analyzer (Roche Diagnostics) using a calibrator traceable to isotope dilution mass spectrometry.[13] The Taiwanese modification of the Modification of Diet in Renal Disease is developing but has not yet published. Therefore, the value of eGFR was calculated using the 4-variable equation in the Modification of Diet in Renal Disease study.[14] The equation was eGFR $mL \cdot min^{-1} \cdot 1.73\ m^{-2} = 186 \times$ serum creatinine $^{-1.154} \times$ age $^{-0.203} \times 0.742$ (if female). Proteinuria was examined by dipsticks (Hema-Combistix; Bayer Diagnostics, Dublin, Ireland). A test result of 1+ or more was defined as positive. Blood and urine samples were obtained within 1 month of enrollment. In addition, information regarding patient medications including angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), β-blockers, calcium channel blockers, diuretics and erythropoiesis-stimulating agents (ESA) during the study period was obtained from medical records.

Assessment of Rate of Renal Function Decline

The rate in renal function decline was assessed by the eGFR slope, defined as the regression coefficient between eGFR and time in unit of milliliters·per minute per 1.73 m^2·per year. At least 3 eGFR measurements after echocardiographic examination were required to estimate eGFR slope. In patients reaching dialysis, renal function data were censored. The other patients were followed until February 2011.

Definition of Cardiovascular Events

Cardiovascular events were defined as cardiovascular death, hospitalization for unstable angina, nonfatal myocardial infarction, sustained ventricular arrhythmia, hospitalization for congestive heart failure, transient ischemia attack and stroke. Cardiovascular events were ascertained and adjudicated by cardiologists from the hospital course and medical record. In patients reaching cardiovascular events, they were followed until the first episode of cardiovascular events. The other patients were followed until February 2011.

Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS, Inc, Chicago, IL) for windows. Data are expressed as percentages, mean ± standard deviation, mean ± standard error of mean for eGFR slope or median (25th–75th percentile) for triglyceride and number of serum creatinine measurements.

The study patients were stratified into 4 groups according to sex-specific median values of hemoglobin and with/without LVH. Multiple comparisons among the study groups were performed by one-way analysis of variance followed by post hoc test adjusted with a Bonferroni's correction. The relationship between 2 continuous variables was assessed by a bivariate correlation method (Pearson's correlation). Linear regression analysis was used to identify the factors associated with decline in kidney function. Time to the cardiovascular events and covariates of risk factors were modeled using Cox's proportional hazards model. Survival curve for cardiovascular events was derived using Cox's regression analysis. Significant variables in univariate analysis were selected for multivariate analysis. A difference was considered significant if the P value was less than 0.05.

RESULTS

The comparison of clinical characteristics among the study groups is shown in Table 1. A total of 415 patients with nondialyzed CKD were included. There were 95, 58, 115 and 147 patients in 4 groups, respectively. The mean age was 66.6 ± 12.1 years, and there were 265 males and 150 females. The values of eGFR slope of all patients were −1.58 ± 0.14 $mL \cdot min^{-1} \cdot 1.73\ m^{-2} \cdot$year. The average number of serum creatinine measurements during the follow-up period was 8 (25th–75th percentile: 6–12) times (range, 3–30). The underlying etiology of CKD in our patients included 219 with diabetic kidney disease (52.8%), 124 with nondiabetic glomerular diseases (29.9%), 38 with tubulointerstitial diseases (9.2%), 27 cases of hypertension (6.5%) and 7 caused by other diseases (1.7%). The median values of hemoglobin level were 12.7 mg/dL in males and 10.5 mg/dL in females, respectively. The level of hemoglobin was inversely correlated with LVMI ($r = -0.189$, $P < 0.001$). Compared with patients without ESA use, patients with ESA use had lower hemoglobin (9.4 ± 1.7 versus 11.9 ± 2.2 g/dL, $P < 0.001$) and lower eGFR (6.4 ± 1.6 versus 29.0 ± 13.1 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, $P < 0.001$). Figure 1 illustrates the eGFR slopes among 4 study groups. The eGFR slopes in 4 groups were −0.59 ± 0.23, −1.49 ± 0.36, −1.05 ± 0.26 and −2.66 ± 0.23 $mL \cdot min^{-1} \cdot 1.73\ m^{-2} \cdot$yr, respectively. The eGFR slope was lower in the group with lower hemoglobin and LVH than in the other groups ($P \leq 0.031$).

Risk of Rapid Renal Function Decline

Table 2 shows the determinants of eGFR slope in all patients. Faster renal function progression had larger negative value of slope. In the univariate analysis, the eGFR slope had a significantly positive correlation with albumin, baseline eGFR and LVEF and negative correlation with diabetes mellitus, cerebrovascular disease, congestive heart failure, systolic and diastolic blood pressures, pulse pressure, the groups with lower hemoglobin but without LVH and lower hemoglobin and LVH (versus higher hemoglobin and without LVH), fasting glucose, total cholesterol, phosphate, uric acid, proteinuria, calcium channel blocker use and diuretic use. In the multivariate analysis, the eGFR slope was correlated independently with diastolic blood pressure, the group with lower hemoglobin and LVH ($\beta = -0.163$; $P = 0.017$), albumin, total cholesterol, uric acid, proteinuria, diuretic use and LVEF. The results indicated high diastolic blood pressure, the group with lower hemoglobin and LVH, low albumin, high total cholesterol, high uric acid, proteinuria, diuretic use and low LVEF had faster progression of renal function.