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Original article

Chronic kidney disease, inflammation, and cardiovascular disease risk in rheumatoid arthritis

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ABSTRACT

Background: Rheumatoid arthritis (RA), a prototypic systemic autoimmune inflammatory condition, confers an increased risk of cardiovascular disease (CVD). Recently, chronic kidney disease (CKD) was suggested to increase the risk of CVD in RA patients, and inflammation was identified as a critical, nontraditional CKD-associated risk factor for CVD. This study aimed to examine the combined effects of CKD and CVD in RA patients.

Methods: In this retrospective evaluation of 428 RA patients, the outcome of interest was the incidence of CVD. CKD was defined as an estimated glomerular filtration rate of $<$60 mL/min/1.73 m^2 and/or positive dipstick tests for proteinuria of $\geq$3 months duration. C-reactive protein (CRP) was used as an inflammation marker, and a high CRP level was defined as a mean CRP value of $\geq$0.57 mg/dL during the first 6 months of follow-up. Patients were categorized as follows: non-CKD with low CRP, non-CKD with high CRP, CKD with low CRP, and CKD with high CRP.

Results: During a median follow-up of 89 months, 67 patients (16%) had CKD, and 38 (9%) developed CVD. Using patients with non-CKD and low CRP as a reference group, the adjusted hazard ratios (HR, 95% confidence interval) for CVD were 1.88 (0.25–9.44) for patients with CKD/low CRP and 9.71 (3.27–31.97) for those with CKD/high CRP.

Conclusions: The coexistence of CKD and inflammation was associated with a higher risk of CVD than either condition alone in RA patients. Inflammation might increase the risk of CVD especially in patients with CKD.

Introduction

Patients with rheumatoid arthritis (RA), a prototypic autoimmune disease characterized by chronic systemic inflammation, face an increased risk of cardiovascular disease (CVD) [1–5]. Currently, the reported incidence of CVD is >50% higher among RA patients than in the general population [6,7]. Although both traditional cardiovascular (CV) risk factors and inflammation contribute to this increased CVD risk [4], the mechanism underlying this process remains unclear.

Chronic kidney disease (CKD), known as an independent risk factor for CVD in the general population [8–12], is a frequent comorbidity among RA patients [13,14] and was recently suggested to increase the risk of CVD in this population [15,16]. Inflammation, an atherosclerotic factor, is a manifestation of CVD [17] and is considered an untraditional CV risk factor in CKD patients [17–21]. Notably, inflammation has been described as a potential primary mediator or "missing link" to explain the tremendous burden of CVD experienced by CKD patients [18]. Despite the associations of chronic inflammation with CV mortality and morbidity in RA patients [2,22–24], it remains unclear whether inflammation also affects the mechanisms underlying the high risk of CVD in CKD among this population. The present study therefore aimed to examine the combined effects of CKD and inflammation, indicated by the

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marker C-reactive protein (CRP), on CVD development in RA patients.

Materials and methods

Participants

This retrospective study of digital medical records from Tomishiro Central Hospital (Okinawa, Japan) was conducted after obtaining permission from the Ethical Committee of Tomishiro Central Hospital. Prior to accession for this study, the data from medical records were anonymized.

As a baseline, we screened 487 adult patients (older than 18 years) who visited the hospital in April 2006 and met the American College of Rheumatology 1987 criteria [25]. We excluded patients with missing clinical data ($n = 57$) and those receiving maintenance hemodialysis ($n = 2$) to yield a population of 428 patients. This final population was reviewed retrospectively to determine the incidence rates of CVD, death, and loss to follow-up until the end of the study (March 31, 2014).

Procedure

Nurses or doctors in the outpatient department administered a lifestyle and medical history questionnaire to study participants, collected blood and urine samples, and measured blood pressure levels. CKD was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 and/or the presence of proteinuria for ≥ 3 months, according to the criteria of the Japanese Society of Nephrology [26]. The following risk factors for CVD were defined: hypertension, more than two resting blood pressure measurements of ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic or treatment with antihypertensive agents; diabetes mellitus, at least two measured fasting plasma glucose levels ≥ 126 mg/dL, a 2-h plasma glucose level ≥ 200 mg/dL, or treatment with hypoglycemic agents; and dyslipidemia, a low-density lipoprotein cholesterol level ≥ 140 mg/dL, high-density lipoprotein cholesterol level <40 mg/dL, triglyceride level ≥ 150 mg/dL, or treatment with specific lipid-lowering agents, according to the criteria of the Japan Atherosclerosis Society [27].

The clinical characteristics of RA were assessed based on medical records. These parameters included the disease duration and the continuous use of anti-rheumatic medication, including methotrexate (MTX), other disease modifying anti-rheumatic drugs (DMARDs: bucillamine, sulfasalazine, D-penicillamine, auranofin, actarit, mizoribine, tacrolimus, and leflunomide), biological agents, corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs), for ≥ 6 months during the interval between the first and third CRP measurements.

The eGFR was calculated using the Japanese Society of Nephrology formula [28]:

$$\text{eGFR (mL/min/1.73 m}^2) = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} (\times 0.739, \text{ if female})$$

The serum creatinine level was measured using an enzymatic method (Sekisui Medical, Tokyo, Japan). Proteinuria was defined as a dipstick urinalysis score of 1+ or higher (Eiken Chemical, Tokyo, Japan). CRP levels were measured using the Nanopia CRP test, which was based on a latex agglutination immunoassay method (Sekisui Medical) and had a normal assay range of ≤ 3 mg/L. Blood glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were determined using a HITACHI 7170 autoanalyzer (Hitachi, Tokyo, Japan). Rheumatoid factor was measured using a latex agglutination test (Mitsubishi Kagaku Iatron, Tokyo, Japan).

Subgroups by CKD and CRP data

CRP is an acute-phase reactant protein produced in response to many inflammatory conditions. Given the chronic inflammatory nature of RA, however, we used the mean CRP values during the first 6 months of follow-up to diagnose a sustained inflammatory state. Accordingly, we measured CRP at three time points, at baseline and at 3 (range: 2–4 months), and 6 months (range: 5–7 months) from the baseline, and calculated the mean CRP value for each patient. A high mean CRP value was defined as exceeding their median values, whereas a low value was defined as below their median values. Patients were subsequently categorized into four groups according to the CKD status and CRP value to examine the combined effect of these parameters: non-CKD with low CRP, non-CKD with high CRP, CKD with low CRP, and CKD with high CRP.

Outcome

For this analysis, the primary outcomes were hospitalization for fatal or nonfatal coronary heart disease (CHD), congestive heart failure (CHF), or stroke. The diagnostic accuracy of our review of the medical records was confirmed using the following criteria. CHD diagnoses were based on the following information: presence of chest pain, abnormal cardiac enzymes, evolving diagnostic electrocardiogram changes, and/or morphologic changes, including local asynergistic cardiac wall motion on echocardiography. CHF was defined according to the Framingham criteria [29]. Stroke was defined as the sudden onset of an inconclusive and focal neurologic deficit persisting for >24 h, and new findings on brain computed tomography or magnetic resonance imaging.

Statistical analysis

Student's unpaired t test (parametric distributions) or the Mann–Whitney test (nonparametric distributions) was used as appropriate for the comparative analyses of CKD subgroups. Parametric analyses to determine intergroup differences in discrete variables among the four CKD/CRP subgroups were conducted using an analysis of variance, followed by the Tukey–Kramer post hoc test. Nonparametric analyses were conducted using the Kruskal–Wallis test with the Steel–Dwass test. Cumulative event-free survival rates were calculated using the Kaplan–Meier method, and intergroup differences were assessed using the log-rank test. Patients were censored from this analysis at the time of an event (including death), loss to follow-up, or the end of follow-up, whichever came first.

A Cox proportional hazard analysis was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD development in both crude and adjusted models. We further calculated the HRs for CVD among the CKD/CRP subgroups. The following covariates were included in the adjusted models: age (10-year increments), sex, and traditional CV risk factors, including CVD history (yes/no), hypertension (yes/no), diabetes mellitus (yes/no), dyslipidemia (yes/no), and smoking status (ever/never). The effects of interactions between CKD and high CRP on CVD were tested by entering the two independent variables and their product term into the same model, and beginning the time intervals for the cumulative event-free survival curves and Cox proportional hazard analysis after the third CRP measurement.

Statistical analyses were performed using the JMP software package (SAS Institute Inc., Cary, NC, USA). Continuous data are expressed as means $\pm$ standard deviations, whereas skewed distributions are presented as medians with 25th and 75th percentiles. A p-value < 0.05 was considered statistically significant.

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