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Relationship of rheumatoid arthritis and coronary artery disease in the Korean population: a nationwide cross-sectional study

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Abstract

Background: Rheumatoid arthritis (RA) is known to be associated with coronary artery diseases (CAD). Previous studies of the association between RA and CAD were reported mainly in non-Asian groups. We aimed to examine the prevalence of RA and the relationship between RA and CAD in South Korea.

Methods: We conducted a nationwide cross-sectional study by using the Korea National Health and Nutrition Examination Survey, which collected data for four years between 2008 and 2012. A total of 25,828 eligible participants were included. To balance the distribution of baseline characteristics, we used propensity score-matching. A multivariable logistic regression model was employed and we calculated the odds ratios (ORs) and 95% confidence intervals (CI) for the odds of the participants with RA on CAD prevalence.

Results: The prevalence of RA in Korea from 2008 to 2012 was 0.6% and RA was predominant among elderly women. The prevalence of CAD in patients with RA was significantly higher than in general population. After propensity score-matching to balance the confounding factors, RA was significantly associated with CAD (OR 2.97, 95% CI 1.15–7.68, $P = 0.02$).

Conclusions: The prevalence of RA in South Korea was comparable to the worldwide data, and the presence of CAD in RA patients was more than two-fold.

Keywords: Rheumatoid arthritis, Prevalence, Angina pectoris, Myocardial infarction

Background

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease and has been known to increase the risk of cardiovascular diseases (CVD) [1]. RA is associated with increased risks of myocardial infarction (MI), and considered as an independent risk factor for coronary artery diseases (CAD) [2]. Interestingly, clinical manifestations of CAD in patients with RA are somewhat different from those in the general population. CAD in patients with RA presents earlier, silently, and suddenly [3]. Several mechanisms have been introduced to explain these associations beyond traditional cardiovascular (CV) risk factors such as age, sex, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, obesity, and smoking [4, 5]. The inflammatory pathways have been proposed to be involved in the pathogenesis of both diseases by many in vivo and in vitro studies [6–8]. Additionally, genetic factors are known to enhance the CV risks in RA [9].

Although the relationship between RA and CAD is not fully explained, RA accelerates the process of atherosclerosis and worsens the CV outcomes [10]. Recent meta-analysis showed that CVD mortality in patents with RA is higher than that in the general population [11]. Hence, assessment of CV risks in patients with RA is important, and management of CAD is an essential

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part of RA treatment. However, CV risks in RA could differ according to race, and the need for population-specific CAD risk stratification in RA was proposed [12]. Epidemiologic studies investigating relationship between RA and CAD have been reported globally and shown different prevalence among the nations [13, 14]. Unfortunately, the association between RA and CAD were reported mainly in non-Asian groups and no data in South Korea have been reported yet [1, 2, 14]. Since some Asians appeared to have a higher risk for CAD, it is necessary to investigate whether CAD is more common in Korean RA patients than in non-RA patients [15]. We, therefore, investigated the prevalence of RA and the association between RA and CAD in South Korea using nationwide data.

Methods

Study design and population

We conducted a nationwide cross-sectional study by using the Korea National Health and Nutrition Examination Survey (KNHANES), which collected data for four years between 2008 and 2012. Voluntary participants, who provided written informed consents, were included in the KNHANES. The Korean Ministry of Health and Welfare conducted the KNHANES, which was a nationwide cross-sectional study. Households were randomly selected for participation, and sampled multi-stage stratification was based on geographical areas. The KNHANES was conducted in accordance with the Helsinki Declaration of 2000. The samples were determined by the household registries of the 2005 National Census Registry.

A total of 36,853 individuals participated in the 2008–2012 KHANES. A total of 11,025 participants who did not complete the health survey section regarding age, smoking, alcohol drinking, RA, HTN, DM, and/or dyslipidemia were excluded. Thus, the total number of eligible individuals was 25,828.

Main variables and covariates

The current diagnosis of RA was based on the self-reported data in response to the questions "Was your RA diagnosed by a physician" and "Are you being treated for RA?" The response was either "Yes" or "No." The participants who responded "Yes" to both questions were considered as RA patients. The presence of CAD was based on a "Yes" response to the questions, "Was your angina pectoris or MI diagnosed by a physician" and "Are you currently being treated for angina pectoris or MI?" Alcohol consumption status was defined as follows: 1) heavy drinkers (consumed an average of ≥ 7 units of alcohol for men and ≥ 5 units for women ≥ 2 days/week), 2) moderate drinkers (consumed more than one glass of alcohol per month over the past year), and 3) nondrinkers (never drank or had drunk less than one glass of alcohol per month over the past year) [16]. The smoking group comprised current smokers, and the nonsmoking group comprised former smokers and those who had never smoked. For obesity classification, we classified the participants into three groups: 1) low weight group for body mass index (BMI) lower than 18.5 kg/m^2, 2) normal weight group for BMI between 18.5 and 25 kg/m^2, and 3) obese group for BMI higher than 25 kg/m^2, according to the guidelines of Korean practice [17]. HTN was defined as average systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or taking of antihypertensive medications. Systolic and diastolic blood pressure was measured by standard methods using a sphygmomanometer while the patient was seated. Three measurements were recorded for all subjects at 5-min intervals, and the average of the second and third measurements was used in the analysis. We defined dyslipidemia as follows: hypercholesterolemia, total cholesterol ≥ 200 mg/dl; hypertriglyceridemia, triglyceride ≥ 150 mg/dl; and hypo-high-density lipoprotein-cholesterolemia (HDL-C), < 40 mg/dL in men, < 50 mg/dL in women, or currently taking any anti-dyslipidemic drug for the purpose of controlling blood lipid concentrations. Low-density lipoprotein cholesterol (LDL-C) concentration was calculated according to the Friedewald equation, after the exclusion of participants whose triglyceride concentrations exceeded 350 mg/dl. DM was defined as a fasting plasma glucose (FPG) level ≥ 126 mg/dL, diagnosis of DM by a clinician, or taking of an oral hypoglycemic agent or injected insulin.

Statistical analysis

According to the Korea Ministry of Health and Welfare and Korea Centers for Disease Control & Prevention guidelines, we used the survey-weighted statistical analyses. Chi-square or Fisher's exact tests were used to compare for categorical variables, t-tests for normal distribution, and Kruskal-Wallis tests for non-normal distribution of continuous variables to compare the demographic variables. We calculated the odds ratios (ORs) and 95% confidence intervals (CI) for CAD risk according to RA. We used the multivariable logistic regression model in which we adjusted for the confounding variables of age, sex, alcohol consumption and smoking status, BMI, HTN, dyslipidemia, and DM. The SPSS ver. 23.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses, and the IBM SPSS Statistics Version 23 - Essentials for R Version 23.0.0 (SPSS Inc., Chicago, IL, USA) was used for propensity score-matched analysis. A P value < 0.05 was considered significant.

Propensity score-matching

To balance the distribution of baseline characteristics, we used propensity score-matching. We estimated a

propensity score for each study participant using the multivariable logistic regression model. In the model, potential confounders and variables associated with CAD, such as age, sex, alcohol consumption and smoking status, BMI, HTN, dyslipidemia, and DM were included. We then created an exchangeable comparison group of the patients with RA by matching each with one patient without RA. Our propensity score model discriminated well between the RA and non-RA groups. The model was fit to the data during all steps of the regression analyses (Hosmer and Lemeshow goodness-of-fit test $\chi^2 = 4.56$; $P = 0.95$, and relative multivariate imbalance L1 after matching = 0.714). We then used the propensity score to match each patient with RA to another patient without RA, who had a similar propensity score, matching 238 of those patients with RA to another 238 patients without RA. Our assessment of the covariate balance after matching focused on these standardized differences. Before matching, the mean propensity score for the patients with RA was 0.009, and for the patients without RA was 0.022. After matching, the mean propensity score for the patients with RA was 0.022, and for the patients without RA was 0.022.

Results

Prevalence of RA

Of the 25,828 KNHANES participants included in the present study, 10,915 were men (42.3%), 14,913 were women (57.7%), and 238 were patients with RA (0.9%). Baseline patient characteristics between the RA and non-RA groups were significantly different (Table 1). Old age and female gender were dominant in the RA group. While non-drinkers were more in the RA group, current smoker was more in the non-RA group. Prevalence of HTN, dyslipidemia, DM, and CAD were also higher in RA group than in the non-RA group. The overall adjusted prevalence of RA in Korea from 2008 to 2012 was 0.6% (95% CI 0.5–0.7%). The prevalence of RA increased with age (Table 2).

Association between RA and CAD

After propensity score-matching for all confounding variables such as age, sex, alcohol consumption, smoking status, BMI, HTN, dyslipidemia, and DM, baseline characteristics in the two groups were similar (Table 3). In an analysis with propensity score-matching, the prevalence of CAD was significantly higher in RA patients (OR 2.97, 95% CI 1.15–7.68, $P = 0.02$; Table 4).

Discussion

This nationwide study investigated the prevalence of RA in Korea and the association between RA and CAD. In this study, the prevalence of RA in Korea from 2008 to 2012 was 0.6%. RA was dominant among the aged women, and patients in the RA groups had more frequencies of HTN, dyslipidemia, and DM. Although smoking is known to be a risk factor for RA, in this study, current smokers were more common in the non RA group. This result is probably due to the fact that

Table 1 Baseline characteristics of the study participants

Variables	Frequency			Weighted frequency*		
	RA group $n = 238$	Non-RA group $n = 25,590$	P	RA group $n = 938,122$	Non-RA group $n = 147,771,248$	P
Age, years†	64.40 ± 13.17	49.87 ± 16.67	< 0.001	61.39 ± 14.71	44.96 ± 15.96	< 0.001
Female sex, n (%)	201 (84.5)	14,712 (57.5%)	< 0.001	801,097 (85.4)	74,517,785 (50.4%)	< 0.001
Alcohol Intake			< 0.001			< 0.001
Nondrinker, n (%)	219 (92.0)	20,159 (78.8)		851,124 (90.7)	112,482,020 (76.1)	
Moderate drinker, n (%)	13 (5.5)	3560 (13.9)		58,045 (6.2)	24,128,683 (16.3)	
Heavy drinker, n (%)	6 (2.5)	1871 (7.3)		28,953 (3.1)	11,160,544 (7.6)	
Current smoker, n (%)	19 (8.0)	5265 (20.6)	< 0.001	79,400 (8.5)	37,895,669 (25.6)	< 0.001
Degree of obesity			0.43			< 0.001
Low, n (%)	11 (4.6)	1189 (4.6)		50,925 (5.4)	7,230,860 (4.9)	
Normal, n (%)	142 (59.7)	16,262 (63.5)		552,121 (58.9)	93,306,408 (63.1)	
Obese, n (%)	85 (35.7)	8139 (31.8)		335,076 (35.7)	47,233,980 (32.0)	
Hypertension, n (%)	93 (39.1)	5643 (22.1)	< 0.001	335,843 (35.8)	25,000,131 (16.9)	< 0.001
Dyslipidemia, n (%)	33 (13.9)	2466(9.6)	0.03	120,048 (12.8)	11,675,583 (7.9)	< 0.001
Diabetes mellitus, n (%)	42 (17.6)	2087 (8.2)	< 0.001	171,300 (18.3)	9,271,183 (6.3)	< 0.001
Coronary artery disease, n (%)	17 (7.1)	452 (1.8)	< 0.001	62,174 (6.6)	1871,935 (1.3)	< 0.001

†Data are presented as mean ± standard deviation
*Weighted population according to individual weight provided by national surveys
RA: rheumatoid arthritis

Table 2 Prevalence of rheumatoid arthritis in Korea

Age	Prevalence of RA		Weighted prevalence of RA, n (%)	
	Female, n (%)†	Overall, n (%)‡	Female, n (%)†	Overall, n (%)‡
Overall age	201 (84.5)	238 (0.9)	801,096 (85.4)	938,122 (0.6)
Age, years				
< 40	12 (80.0)	15 (0.2)	69,025 (81.6)	84,589 (0.1)
40–49	16 (88.9)	18 (0.4)	100,034 (87.2)	114,741 (0.4)
50–59	30 (85.7)	35 (0.8)	144,675 (81.2)	178,109 (0.7)
60–69	61 (89.7)	68 (1.6)	190,633 (90.2)	211,309 (1.3)
≥ 70	82 (80.4)	102 (2.6)	296,729 (84.9)	349,374 (2.6)

†Data show the percentage of female
‡Data show the proportion with RA in the total population
RA: rheumatoid arthritis

most of the RA patients were middle-aged women and smoking prevalence of middle-aged women is low in Korea. The prevalence of CAD in patients with RA was significantly higher than in general population. After the propensity score-matching, RA was significantly correlated with CAD.

Epidemiologic studies investigating RA showed a prevalence of 0.3–6.0%, which varied according to their countries [18–23]. An averaged prevalence of 0.5–1.1% was reported in the European and general populations of the United States; however, native Americans showed a higher prevalence of 5.3–6.0% [13]. Studies carried out in developing countries reported a lower RA prevalence of 0.1–0.5%. In Asia, most studies reported a prevalence of 0.1–0.3%; in contrast, one previous study suggested a relatively higher prevalence of 2.0–4.7% [24]. In this study, the prevalence of RA was 0.6%, which was comparable to that of the western population but higher than that of the other Asian populations. Early diagnosis of RA and higher life expectancy in Korea than in other Asian countries is considered to be responsible for the increased prevalence of RA.

The prevalence of RA was generally two to threefold higher in women [13]. In this study, RA was more prevalent in women; the sex ratio was about 4:1, with greater predominance in women than reported in other studies. Majority of the studies also revealed that RA onset peaked in the fifth decade or later [25–28]. In this study, the prevalence of RA increased with age; however, the exact disease onset could not be assessed.

We have shown that the prevalence of CAD in RA patients was higher than in non-RA patients using propensity score-matching. Previous studies reported that RA directly affected the coronary arteries and raised the risk of CVD by 2-fold [29, 30]. A recent study investigating co-morbidities in patients with RA suggested that the prevalence of CAD might be increased in Korean patients with RA [31]. In our study, we assessed and compared the risks of CAD on RA, using propensity-score matching between patients with RA and without RA. Therefore, we consider that this study is novel in assessing the risks of CAD on RA in an Asian population.

Regarding the relationship between RA and CAD, traditional risk factors could not fully explain the elevated risk of CVD in patients with RA. In addition to traditional risk factors, nontraditional risk factors were additively associated with atherosclerosis and CVD in RA patients. The most likely mechanism is high-grade inflammation in RA. Studies investigating the relationship between RA and CAD suggested a direct link between the degree of inflammation and the risk of CV events [32]. Pro-inflammatory cytokines, such as tumor necrosis factor-α and interleukin-6 were well known to contribute to atherosclerosis development and played an

Table 3 Baseline characteristics of the study participants after propensity score-matching

Variables	RA group	Non-RA group	*P*
	n = 238	n = 238	
Age, years†	64.40 ± 13.17	64.07 ± 13.32	0.79
Female sex, n (%)	201 (84.5)	201 (84.5)	0.99
Alcohol Intake			0.48
Nondrinker, n (%)	219 (92.0)	225 (94.5)	
Moderate drinker, n (%)	13 (5.5)	10 (4.2)	
Heavy drinker, n (%)	6 (2.5)	3 (1.3)	
Current smoker, n (%)	19 (8.0)	20 (8.4)	0.99
Degree of obesity			0.83
Low, n (%)	11 (4.6)	14 (5.9)	
Normal, n (%)	142 (59.7)	140 (58.8)	
Obese, n (%)	85 (35.7)	84 (35.3)	
Hypertension, n (%)	93 (39.1)	97 (40.8)	0.78
Dyslipidemia, n (%)	33 (13.9)	43 (18.1)	0.26
Diabetes mellitus, n (%)	42 (17.6)	37 (15.5)	0.62
Coronary artery disease, n (%)	17 (7.1)	6 (2.5)	0.03

† Data are presented as mean ± standard deviation
RA: rheumatoid arthritis

Table 4 Influence of rheumatoid arthritis on coronary artery disease

Variables	OR before PS-matching			OR after PS-matching		
	OR	95% CI	*P* for trend	OR	95% CI	*P* for trend
RA[†]	4.28	2.59–7.07	< 0.001	2.97	1.15–7.68	0.02
Age	1.08	1.07–1.08	< 0.001	1.05	1.01–1.10	0.01
Female sex	0.69	0.57–0.83	< 0.001	1.98	0.46–8.65	0.36
Alcohol Intake						
Nondrinker	1.00			1.00		
Moderate drinker	0.54	0.39–0.76	< 0.001	–	–	–
Heavy drinker	0.99	0.70–1.40	0.95	–	–	–
Current smoker	0.60	0.46–0.78	< 0.001	1.07	0.24–4.75	0.93
Degree of obesity						
Low	1.00			1.00		
Normal	2.04	1.05–3.98	0.04	0.56	0.12–2.61	0.46
Obese	3.49	1.78–6.81	< 0.001	0.57	0.11–2.86	0.50
Hypertension	5.71	4.73–6.89	< 0.001	3.67	1.48–9.09	0.005
Dyslipidemia	4.79	3.90–5.88	< 0.001	4.51	1.90–10.71	< 0.001
Diabetes mellitus	4.78	4.77–4.79	< 0.001	4.28	1.81–10.15	< 0.001

[†]Adjusted for age, sex, alcohol intake and smoking status, body mass index, hypertension, dyslipidemia and diabetes mellitus
RA: rheumatoid arthritis; PS: propensity score; OR: odds ratio; 95% CI: 95% confidence interval

important role in accelerating atherosclerosis in patients with RA [33]. Indeed, high-grade inflammation could increase metabolic risks such as insulin resistance, and directly impair endothelial function. Endothelial dysfunction promoted by such pro-inflammatory cytokines was characterized by decreased nitric oxide bioavailability [34, 35]. Further, oxidative stress and T cells were suggested to play a key role in inflammation and atherosclerosis development in patients with RA [36]. A recent study on anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab suggests that reducing inflammation without affecting lipid levels reduces the risk of cardiovascular disease [37]. Consequently, further investigation of the role of anti-inflammatory therapy in patients with RA and CAD is required.

Some limitations are present in this study. First, the cross-sectional design precludes conclusions about causal relationships; thus, further prospective studies and intervention trials should be undertaken to establish a causal association between RA and CAD. The relationship of RA to CAD is important, since these two diseases possess common inflammatory pathways. Second, the current diagnostic status of RA and CAD was based on self-reports. Consequently, these data may have been influenced by systematic errors in individuals' consideration, which may have led to non-differential misclassification or overestimation. In particular, osteoarthritis (OA) can be confused with RA. However, in case of OA diagnosis in KNHANES, it is possible to prevent misdiagnosis to some extent because OA diagnosis was based on patients' pain and radiologic examinations.

Conclusions

The present study found that the prevalence of RA was 0.6%, which was similar to that reported worldwide, and the presence of RA was associated with an approximately 2-fold increased prevalence of CAD. Therefore, patients with RA would be better to be examined for CAD for early diagnosis and management.

Abbreviations

BMI: body mass index; CAD: coronary artery diseases; CVD: cardiovascular diseases; DM: diabetes mellitus; FPG: fasting plasma glucose; HDL-C: high-density lipoprotein-cholesterol; HTN: hypertension; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction; OA: osteoarthritis; RA: rheumatoid arthritis

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Authors' contributions

THL: Study design; Manuscript preparation; Elaboration of article; Data analysis and interpretation. GGS: Elaboration of article and critical review; Data analysis and interpretation. SJC: Elaboration of article and critical review; Data analysis and interpretation. HS: Data collection; Data analysis and interpretation. JHJ: Study design; Manuscript preparation; Elaboration of article and critical review; Data interpretation. All authors read and approved the final manuscript to be published.

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Availability of data and materials

The datasets generated during the current study are available in the KNHANES repository, http://www.cdc.go.kr/CDC/contents/CdcKrContentView.jsp?cid=60939&menuIds=HOME001-MNU1130-MNU1639-MNU1748-MNU1751.

Ethics approval and consent to participate

All participants in Korea National Health and Nutrition Examination Survey (KNHANES) signed an informed consent form and the institutional review board of the Korea Centers for Disease Control and Prevention approved the study (IRB: 2008-04EXP-01-C, 2009-01CON-03-2C, 2010-02CON-21-C, 2011-02CON-06-C, 2012–01 EXP-01-2C). The survey was conducted in accordance with the 2000 Declaration of Helsinki principles. Informed consent was waived because this study performed secondary analysis using the KNHANES dataset.

Consent for publication

All authors consent to publish the manuscript in Advances in Rheumatology.

Competing interests

The authors declare that they have no competing interests.

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