Journal of Rheumatic Diseases
Vol. 21, No. 3, June, 2014
http://dx.doi.org/10.4078/jrd.2014.21.3.132

□ Original Article □

Association between Vitamin D Deficiency and Carotid Intima-media Thickness in Patients with Rheumatoid Arthritis

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Objective. **The present study determined if vitamin D deficiency is a potential risk factor for increased carotid intima-media thickness (CIMT) in patients with rheumatoid arthritis (RA).**

Methods. **This cross-sectional study analyzed 50 consecutive female RA patients without cardiovascular disease history at the Pusan National University Hospital between September and December of 2013. CIMT was measured using a high-resolution ultrasonography. Serum 25-hydroxy vitamin D (25-OHD) levels were assessed by radioimmunoassay, and vitamin D deficiency was defined as serum 25-OHD levels ＜20 ng/mL. Stepwise multivariable linear regression analyses were performed to evaluate the association between vitamin D deficiency and increased CIMT.**

Results. The median 25-OHD level (inter-quartile range) was 14.0 (11.0～20.7) ng/mL, and 74% of patients had vitamin D deficiency. The mean±standard deviation of CIMT was 0.58±0.08 mm. RA patients with vitamin D deficiency had significantly higher CIMT than those without this feature (0.59±0.07 vs 0.54±0.05, p=0.028). In univariable linear regression models, vitamin D deficiency (β(SE)=0.047 (0.021), p=0.028), older age (β(SE)=0.003 (7.2^{-4}), p＜0.001) and higher disease activity score 28-erythrocyte sedimentation rate (β(SE)=0.021 (0.010), p=0.034) and Korean version of health assessment questionnaire score (β(SE)=0.051 (0.015), p=0.002) were significantly associated with increased CIMT. Vitamin D deficiency remained statistically significant in multivariable regression models after adjusting for confounders.

Conclusion. **Vitamin D deficiency was associated with increased CIMT in female RA patients. Our finding suggests that hypovitaminosis D can be a risk factor for atherosclerosis in RA patients.**

Key Words **Vitamin D, Rheumatoid arthritis, Atherosclerosis, Cardiovascular diseases**

Introduction

Increasing evidence indicates that low serum 25-hydroxy vitamin D (25-OHD) is associated with a higher frequency of cardiometabolic outcomes including type 2 diabetes mellitus, hypertension, and cardiovascular diseases (CVDs) in the general population (1,2). The National Health and Nutritional Examination Surveys (NHANES 2000～2004) revealed that the frequency of CVDs including coronary heart disease, heart failure and peripheral vascular disease are significantly higher in adults with low 25-OHD levels (＜20 ng/mL) than those with high 25-OHD levels (≥30 ng/mL) (3). In addition, limited data suggest that vitamin D supplementation may reduce the risk of CVDs (4,5) and decrease mortality in elderly people (6). Experimental evidence that vitamin D regulates the rennin-angiotensin system (7), inhibits vascular smooth muscle cell proliferation (8) and improves endothelial function inflammation (9) may support the epidemiological relationship between vitamin D deficiency and increased risks of CVDs.

＜Received : April 22, 2014, Revised : May 26, 2014, Accepted : June 19, 2014＞
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pISSN: 2093-940X, eISSN: 2233-4718

Hence, studies demonstrating the contribution of vitamin D deficiency on the burdens of cardiovascular morbidity and mortality have prompted increased awareness.

CVDs are the major causes of mortality and morbidity in patients with RA (10). RA was recently shown to be associated with a 1.48-fold increase in CVDs (11) and a 1.6-fold increase in CVD-related death (12), compared to the general population. Epidemiological studies demonstrated that traditional risk factors such as smoking, hypertension, dyslipidemia, diabetes, and obesity as well as the inflammatory burden of RA can cause premature atherosclerosis and eventually lead to CVD development. As mounting evidence indicating the immunoregulatory effect of vitamin D has prompted several studies investigating the association of hypovitaminosis D with the disease activity and outcomes of RA (13). However, little attention has been given to the association of vitamin D deficiency with atherosclerosis or CVDs in patients with RA. Accordingly, the present study determined if vitamin D deficiency is a potential risk factor for carotid atherosclerosis assessed by carotid intima-meida thickness (CIMT) in patients with RA.

Materials and Methods

Study design and subjects

This cross-sectional study included 50 consecutive female RA patients (aged 18～75 years) from a single outpatient rheumatology clinic of the Pusan National University Hospital in Busan, South Korea between September 2013 and December 2013. Pusan National University Hospital is a tertiary referral center in South Korea and Busan is a harbor city with a temperate climate located in the southeastern part of South Korea at a latitude of 34° north. All RA patients met the American College of Rheumatology 1987 revised classification criteria for RA (14). Patients with previous CVDs, abnormal renal function (serum creatinine ≥1.2 mg/dL), and current use of vitamin D supplements were excluded. All subjects provided written informed consent in accordance with the Declaration of Helsinki prior to study participation. This study was approved by the Research and Ethics Review Board of the Pusan National University Hospital, Busan, South Korea.

Assessments

General information was collected by an interview and review of medical records. Anthropometric parameters including height, weight, body mass index (BMI), waist and hip circumference and blood pressure were measured in all study subjects. BMI was calculated as body weight divided by the square of height in meters (kg/m^2). Waist circumference was measured at the smallest circumference of the natural waist, usually just above the belly button and hip circumference was measured at its widest part of the buttocks or hip. The waist-to-hip ratio (WHR) was subsequently calculated. Blood pressure was determined as the average of two measurements taken at an interval of 5 minutes using a TM-2655P apparatus (A&D Company Ltd., Tokyo, Japan). Hypertension was defined as blood pressure ≥140/90 mmHg or a requirement of antihypertensive medication.

Fasting blood samples of all participants were taken between 8:00 AM and 10：00 AM to determine concentration of total cholesterol (TC), triglycerides (TGs), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), fasting glucose, fasting insulin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and 25-OHD. The concentrations of TC, TGs, and HDL-C were analyzed using an enzymatic colorimetric reagent (Roche Diagnostics, Zurich, Switzerland) and a P800 Module (Roche Diagnostics). LDL-C value was calculated using the Friedewald formula. Fasting glucose and insulin were assessed by the glucose oxidase method (Synchron LX-20, Beckman Coulter Inc., Fullerton, CA, USA) and radioimmunoassay (Diagnostic Product Co., Los Angeles, CA, USA), respectively. CRP was measured with a particle-enhanced immunoturbidimetric assay (Tina-quant C-reactive protein assay, Roche Diagnostics) using a P800 Module (Roche Diagnostics). Serum 25-OHD levels were measured by a radioimmunoassay kit (DIAsource, Belgium) using a γ-counter (1470 Wizard, PerkinElmer, Turku, Finland). Vitamin D deficiency was defined as a 25-OHD levels less than 20 ng/mL. Insulin resistance was evaluated by homeostatic model assessment-insulin resistance (HOMA-IR), which was calculated with the formula defined by Matthews et al. (15) as follows:

HOMA－IR=[fasting serum insulin (μIU/mL)×fasting serum glucose (mg/dL)×0.055/22.5]

The following additional data were collected: disease duration, medication records, swollen joint count (SJC), tender joint count (TJC), general health, physical function, immunoglobulin M-rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (anti-CCP; U/mL) and previous history of type 2 diabetes mellitus and dyslipidemia. For RA patients treated with glucocorticoids (GCs), the cumulative dose (in prednisone equivalent) was calculated by multiplying the current daily dose by the number of days for which patients had received GCs since they were first prescribed. General health was assessed using a visual analogue scale (VAS) ranging form 0-100 and physical function was assessed using the Korean Version of health

assessment questionnaire (K-HAQ) (16). Immunoglobulin M-RF was assessed by particle- enhanced immunoturbidometric assay (range 0～14 IU/ml) and anti-CCP was measured using chemiluminescent microparticle immunoassay (range 0～5 U/mL). Disease activity score (DAS) 28-ESR was calculated using the following formula (17):

DAS28－ESRscore=[0.56×√((TJC28))]+[0.28×((STC28))]+(0.70×in ESR)+(0.0014×VAS)

On the same day of blood sampling, CIMT was measured using high-resolution ultrasonography (Philips HD 15, Bothwell, WA, USA) with a 7.5 to 12.5-MHz linear array transducer. The far walls on both sides of the common carotid artery, carotid bulb and internal carotid artery were visualized at the lateral and anterior-oblique angles. CIMT measurements were performed automatically using QLAB's CIMT quantification software (Philips Healthcare, DA Best, The Netherlands), which can enhance the consistency and reliability of measurement (18). The mean of maximal CIMT from all carotid segments was collected from each study subjects. A CIMT ≥0.6 mm was considered as a maker of subclinical atherosclerosis (19,20). Carotid plaque was assessed in the common carotid artery, carotid bulb and internal carotid artery and was defined as a distinct protrusion of ≥50% from the adjacent wall into the vessel lumen.

Statistical analysis

No formal sample size calculation was conducted. Continuous variables are expressed as mean±standard deviation or median (interquartile range) and categorical variables as the number of cases with percentages. The Kolmogorov-Smirnov test was also applied to assess the normal distribution of each continuous variable. For group comparisons, the two-tailed Student's *t* test or the Mann-Whitney U test was used to compare continuous variables, and the chi-squared test or Fisher's exact test was performed to compare categorical variables. Correlation between continuous variables was evaluated by the Spearman correlation test. The primary goal of our study is to investigate the relationship between vitamin D deficiency and CIMT. Thus, the stepwise multivariate linear regression models that included demographic variables such disease duration and variables with $p<0.20$ in the univariate regression analyses were used. Values of $p<0.05$ were considered to indicate statistical significance. All statistical analyses were performed using STATA version 11.1 for Windows (StataCorp LP, College Station, TX, USA) and SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 50 female patients with RA were enrolled in this study. Their baseline characteristics and biomarker levels are summarized in Table 1. Their mean±SD age was 56.0±11.2

Table 1. Baseline demographics of 50 female patients with rheumatoid arthritis

Variables	Total (n=50)	Vitamin D deficiency (n=37)	No vitamin D deficiency (n=13)	p-value
Age, years, mean±SD	56.0±11.2	56.0±11.2	56.0±11.2	0.547
Disease duration, months, median (IQR)	50 (26.5～100)	55 (29.5～104.5)	59 (28～83)	0.991
RF positive, n (%)	36 (87.8%)	26 (86.7%)	10 (90.9%)	1.00
Anti-CCP antibody positive, n (%)	36 (92.3%)	27 (90.0%)	9 (100%)	1.00
ESR, mm/hr, median (IQR)	17 (7～17)	18.5 (7～40.8)	17 (9～26.5)	0.928
CRP, mg/dL, median (IQR)	0.08 (0.02～0.18)	0.08 (0.23～0.02)	0.08 (0.03～0.14)	0.883
DAS28-ESR, mean±SD	2.72±0.98	2.77±1.06	2.63±0.78	0.683
K-HAQ, median (IQR)	0.38 (0～0.91)	0.25 (0～1.1)	0.38 (0～0.75)	0.911
Current medication				
GCs, n (%)	46 (92)			
Cumulative GCs, g, median (IQR)	3.4 (1.0～7.7)			
Methotrexate, n (%)	39 (78)			
Hydroxychlorouqine, n (%)	18 (36)			
Sulfasalazine, n (%)	7 (14)			
Leflunomide, n (%)	8 (16)			
TNF-α inhibitors, n (%)	1 (2)			
25-OHD, ng/mL, median (IQR)	14.0 (11.2～20.7)			
Vitamin D deficiency, n (%)	37 (74%)			

IQR: interquartile range, RF: rheumatoid factor, Anti-CCP antibody: Anti-citrullinated protein antibody, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DAS28: disease activity score 28, GCs: glucocorticoids, K-HAQ: Korean Version of health assessment questionnaire, TNF-α: tumor necrosis factor-alpha, 25-OHD: 25-hydroxy vitamin D.

years and the median (interquartile range, IQR) disease duration was 50 (26.5～100) months. The mean±SD DAS28-ESR score was 2.72±0.98. Twenty-four (48%) patients with RA had remission with a DAS28-ESR score less than 2.6. All of the patients with RA were treated with at least one disease modifying anti-rheumatic drugs (DMARDs), GCs or tumor necrosis factor-alpha (TNF-α) inhibitors. 46 (92%) patients were taking GCs and median (IQR) cumulative dose of GCs was 3.4 (1～7.7) g. The median (IQR) 25-OHD was 14.0 (11.2～20.7) ng/mL and 37 (74%) patients with RA had vitamin D deficiency. There were no differences in age, disease duration, ESR, CRP, DAS28-ESR and K-HAQ scores and the proportion of RF and anti-CCP antibody positivity according the presence or absence of vitamin D deficiency.

Table 2 shows the baseline cardiovascular risk factors of the study subjects. The mean CIMT value was 0.58±0.08 mm and 48% had a CIMT >0.6 mm. Three patients (6%) showed evidence of carotid plaque. The proportion of RA patients with HTN, dyslipidemia and type II diabetes mellitus were 36%, 14% and 12%, respectively. Of note, RA patients with vitamin D deficiency had significantly higher CIMT than those without this feature (0.59±0.07 vs 0.54±0.05, p=0.028). In addition, the proportion of subclinical carotid atherosclerosis (CIMT ≥0.6 mm) in RA patients with vitamin D deficiency

Table 2. Cardiovascular risk factors in study subjects

Variables	Total (n=50)	Vitamin D deficiency (n=37)	No vitamin D deficiency (n=13)	p-value
BMI, kg/m^2, mean±SD	23.1±3.2	23.1±2.9	23.1±3.9	0.994
WHR, mean±SD	0.85±0.06	0.84±0.05	0.88±0.08	0.039
Smoker, n (%)	3 (6%)	1 (2.7%)	2 (15.3%)	0.162
HTN, n (%)	18 (36%)	12 (32.4%)	6 (46.2%)	0.504
SBP, mmHg, mean±SD	126.8±16.1	126.0±14.6	129.2±20.3	0.532
DBP, mmHg, mean±SD	76.4±12.1	75.1±11.2	80.3±14.1	0.182
Dyslipidemia, n (%)	7 (14%)	5 (13.5%)	2 (15.4%)	1.000
LDL-C, mg/dL, mean±SD	115.1±34.7	114.0±32.5	118.0±41.6	0.755
TG, mg/dL, mean±SD	105.6±59.7	105.0±65.7	107.2±40.5	0.909
HDL-C, mg/dL, mean±SD	70.1±18.4	69.6±18.4	71.6±19.0	0.733
Type 2 DM, n (%)	6 (12%)	6 (16.2%)	0 (0%)	0.319
Fasting glucose, mg/dL, mean±SD	90.8±10.3	91.5±11.3	88.9±6.4	0.453
Fasting insulin, μIU/mL, median (IQR)	5.3 (4.4～7.8)	5.1 (4.0～7.9)	6.5 (5.1～7.7)	0.179
HOMA-IR, median (IQR)	1.13 (0.97～1.73)	1.10 (0.93～1.78)	1.42 (1.03～1.69)	0.301
CIMT, mm, mean±SD	0.58±0.08	0.59±0.07	0.54±0.05	0.028
CIMT ≥0.6 mm, n (%)	24 (48%)	22 (59.5%)	2 (15.4%)	0.009
Carotid plague, n (%)	3 (6%)	2 (5.4%)	1 (7.7%)	1.000

BMI: body mass index, WHR: waist-to-hip ratio, HTN: hypertension, SBP: systolic blood pressure, DBP: diastolic blood pressure, LDL-C: low density lipoprotein cholesterol, TG: triglycerides, HDL-C: high density lipoprotein cholesterol, DM: diabetes mellitus, IQR: interquartile range HOMA-IR: homeostatic model assessment-insulin resistance, CIMT: carotid intima-media thickness.

Table 3. Linear regression models for carotid intima media thickness in study subjects

	Univariable analysis		Model 1*		Model 2†	
	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Age, years	0.003 (7.2^{-4})	<0.001	0.003 (6.9^{-4})	<0.001	0.003 (6.6^{-4})	<0.001
Vitamin D deficiency	0.047 (0.021)	0.028	0.044 (0.017)	0.014	0.041 (0.016)	0.017
BMI, kg/m^2	0.005 (0.003)	0.106	0.005 (0.002)	0.032	0.006 (0.002)	0.016
Disease duration, months	1.6^{-4} (1.6^{-4})	0.318				
HDL-C, mg/dL	−0.001 (5.2^{-4})	0.054				
DAS28-ESR	0.021 (0.010)	0.034				
K-HAQ	0.051 (0.015)	0.002			0.044 (0.015)	0.005
			Adjusted R^{2*}=0.421		Adjusted $R^{2\dagger}$=0.550	

BMI: body mass index, HDL-C: high density lipoprotein cholesterol, DAS28: disease activity score 28, ESR: erythrocyte sedimentation rate, K-HAQ: Korean Version of health assessment questionnaire. *Model 1 includes age, vitamin D deficiency, BMI, disease duration, HLD-C and DAS28-ESR. †Model 2 includes age, vitamin D deficiency, BMI, disease duration, HLD-C and K-HAQ.

was significantly higher than in those without this feature (59.5% vs 15.4%, p=0.009).

The results of linear regression analysis for CIMT are shown in Table 3. Univariable analyses showed that older age, vitamin D deficiency and DAS28-ESR scores and K-HAQ scores were significantly associated with increased CIMT. There was a trend between higher HDL-C and increased CIMT, but it did not reach the statistical significance. Because DAS28-ESR and K-HAQ scores were significantly correlated (correlation coefficient=0.387, p=0.007), these variables were included in separate multivariable linear regression models to prevent multicollinearity. The association between vitamin D deficiency and increased CIMT remained statistically significant in multivariable regression models after adjusting for age, BMI, disease duration, HDL-C, and DAS28-ESR and K-HAQ scores (Table 3). In addition, low serum 25-OHD levels were also significantly associated with increased CIMT in the multivariable regression models (data not shown).

Discussion

Little is known about the epidemiological association between hypovitaminosis D and atherosclerosis in patients with RA. In this preliminary study, vitamin D deficiency was significantly associated with increased CIMT in patients with RA even after adjusting for traditional cardiovascular risk factors, disease activity and functional capacity. These results suggest that vitamin D deficiency may be a risk factor for atherosclerosis and CVDs in patients with RA.

To our knowledge, 2 previous studies have evaluated the association between vitamin D deficiency and cardiometabolic risk in patients with RA. Haque et al. (21) reported that serum 25-OHD was significantly associated with HDL-C and inversely associated with HOMA-IR in 179 RA patients. More recently, Goshayeshi et al. (22) reported that vitamin D deficiency was independently associated with metabolic syndrome in 120 RA patients. Similar to the present study, these studies found that vitamin D is linked to cardiometabolic intermediates in RA patients. However, these previous studies did not evaluate CIMT, which is a surrogate marker of atherosclerosis. Increased CIMT increases the risks of myocardial infarction, stroke and peripheral artery disease; therefore it is considered as an important tool for predicting future CVDs (23). Thus, the present study provides more comprehensive information regarding the role of vitamin D deficiency in cardiovascular risk in patients with RA. The results of the present and previous studies collectively suggest that vitamin D deficiency increases the risks of CVDs in patients with RA.

Vitamin D is a steroid hormone involved in calcium and phosphate homeostasis as well as bone metabolism. Moreover, 25-OHD is a marker of "vitamin D status"; it is converted to active 1,25-OH2D by 1-α-hydroxylase. After binding vitamin D receptor (VDR), 1,25-OH2D exerts its biological action. VDR has a broad tissue distribution including immune cells, endothelium, vascular smooth muscle cells and cardiomyocytes. Accordingly, except for bone metabolism, a great deal of attention has recently been given to the role of vitamin D in the immune and cardiovascular systems. Experimental studies showed that vitamin D regulates the renin angiotensin system (7), suppresses vascular smooth muscle cell proliferation (8), improves endothelial function (9) and inhibits myocardial hypertrophy (24). In addition, considering that inflammation is a predisposing factor for atherosclerosis, the anti-inflammatory property of vitamin D may reduce the risk of CVDs. Concordantly, epidemiological studies suggests an association between vitamin D deficiency and CVDs. Vitamin D deficiency is reported to be associated with a increased risk of myocardial infarction (25), stroke (26), peripheral artery diseases (27) as well as cardiovascular mortality (28) in the general population. In addition, hypovitaminosis D is linked to cardiovascular risk factors including hypertension, insulin resistance and type 2 diabetes mellitus as well as surrogate markers for atherosclerosis such as increased CIMT and coronary artery calcium score (CACS) (1, 29～31). However, the clinical implications of vitamin D deficiency in the atherosclerosis or CVDs of RA patients have not been extensively studied to date. Thus, the present results provide insight into the roles of vitamin D deficiency in CVDs in patients with rheumatic diseases.

Inflammatory rheumatic diseases including RA and systemic erythematous lupus has long been known to increase cardiovascular risks (32). Cardiovascular morbidity and mortality are significantly higher among patients with rheumatic diseases than the general population. The main cause of the CVDs is premature atherosclerosis which is attributable to traditional cardiovascular risk factors including type 2 diabetes mellitus and hypertension as well as the inflammatory burden of rheumatic diseases. Therefore, the surveillance and prevention of atherosclerosis in patients with rheumatic diseases are important issues in clinical practice. Clinicians should pay great attention to modify traditional risk factors and control disease activity to reduce comorbidty of CVDs in RA patients. Considering our results, regular monitoring of serum 25-OHD levels and appropriate maintenance of sufficient levels of vitamin D may be needed in the management of patients with RA.

CIMT has become the most commonly used marker of subclinical atherosclerosis in patients with rheumatic diseases including RA (23). A CIMT $\geq$0.6 mm is considered as a marker

of atherosclerosis (19), whereas a CIMT >0.9 mm or the presence of carotid plaque is associated with subclinical organ damage (33). In RA patients, increased CIMT and carotid plaque are predictive of CVDs (34). A recent meta-analysis shows that CIMT is significantly greater in RA patients than the general population and that age, disease duration and pre-existing atherogenic risk factors contributed to increase CIMT (35). Concordant with these previous findings, older age, high BMI and low functional capacity were associated with increased CIMT in the present study. However, disease duration and traditional cardiovascular risk factors including LDL-C, TG and HOMA-IR did not show the significant association with CIMT in our study, possibly because of small sample size or the characteristics of study subjects.

The epidemiological relationship between vitamin D deficiency and atherosclerosis in the present study should be interpreted cautiously, owing to potential reverse causality. Among the various factors that influence vitamin D status in the human body, sun exposure is the primary determinants of serum 25-OHD. Young or physically active subjects tend to have sufficient vitamin D levels, whereas those who are elderly or sedentary owing to chronic illness are prone to vitamin D deficiency. Therefore, serum 25-OHD may represent general health status rather than a causative factor of CVDs. In addition, the degree of systemic inflammation is inversely associated with the circulating levels of vitamin D (36). Thus, serum 25-OHD reflects the acute phase response, similar to ESR or CRP, and may not increase the risks of CVDs or atherosclerosis. Nevertheless, further investigation is required to better understand the association between vitamin D deficiency and CVDs in patients with RA.

Some studies report an association between CVDs and vitamin D deficiency in patients with other rheumatic diseases besides RA. For example, in a study of patients with Behcet's diseases, CIMT was not associated with hypovitaminosis D but vitamin D supplementation improved CIMT (0.56 vs 0.42 mm, p=0.02) (37). Meanwhile, in patients with systemic lupus erythematosus, vitamin D deficiency was not associated with subclinical atherosclerosis assessed by CIMT and CACS (38). The discrepancy in the effect of vitamin D deficiency on CVDs in patients with rheumatic diseases may be attributable to the differences in the methods for assaying serum 25-OHD levels and risk factors for vitamin D deficiency including sun exposure time, latitude and dietary habit; however, these factors were not fully adjusted for in the present or previous studies. In addition, vitamin D metabolism may vary among rheumatic diseases. Therefore, further studies should compare the effects of vitamin D deficiency on CVDs or atherosclerosis among various rheumatic diseases.

This study has some limitations that warrant further discussion. First, the explanatory power of our model is limited by the small sample size. In addition, because only 3 RA patients had carotid plaques, we could not investigate the association between carotid plaque and vitamin D deficiency. Second, 48% of patients with RA in the present study had remission, with DAS-ESR scores less than 2.6 and there were few active RA patients. Thus, the present subjects may not represent of the entire RA population. Third, this study was a single center study, which could have led to a selection bias.

Conclusion

Vitamin D deficiency was significantly associated with increased CIMT in female patients with RA after adjusting for confounding factors in our study. Thus, the results suggest that hypovitaminosis D is a risk factor for subclinical atherosclerosis in patients with RA. Randomized controlled trials demonstrating that vitamin D supplementation reduces the risks of atherosclerosis or future CVDs in patients with RA are required to corroborate the present findings.

Acknowledgements

The authors declare no conflict of interest. We specially thank the late Professor Sung-Il Kim who was devoted himself to education, research and patient care in Division of Rheumatology, Department of Internal Medicine, Pusan National University School of Medicine (1963～2011). This work was supported by clinical research grant form Pusan National University Hospital 2014.

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