Cardiovascular Risk Factors in Filipinos with Rheumatoid Arthritis Included in the Rheumatoid Arthritis Database and Registry (RADAR)

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Abstract

Introduction: Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis of unknown etiology. Cardiovascular disease (CVD) remains a major problem for these patients. This paper aims to describe the presence of cardiovascular risk factors among filipino patients with rheumatoid arthritis seen in the Philippine General Hospital Rheumatology outpatient department. This will also serve as a baseline database for patients with cardiovascular risk factors for future studies on the impact of rheumatoid arthritis on cardiovascular morbidity and mortality. Objective: to describe the presence of cardiovascular risk factors among filipino patients with rheumatoid arthritis seen in the Philippine General Hospital Rheumatology outpatient department included in the Rheumatoid Arthritis Database and Registry (RADAR)

Methods: Cases entered in the study were taken from the RADAR. Included patients were those worked up for traditional and non-traditional cardiovascular risk factors. Demographic data, traditional and nontraditional cardiovascular risk factors and management for RA and CVD were extracted. Descriptive statistics were applied. This study is approved by the Institutional Review Board.

Results: Ninety eight patients were included in this study. Ninety four percent were female with mean age at diagnosis of 49.95±10.17 (SD) years and mean disease duration of 63.01 months. For traditional cardiovascular risk factors: 18% were smokers; 34% (24/71) were obese; mean BMI was 23.85±4.60 (SD) kg/m^2; 39% (38/98) had hypertension of which 87% were on antihypertensive medication; 19% has impaired fasting glucose (IFG) or diabetes and 55% had dyslipidemia but only 53% and 33% were on oral hypoglycemic agents and statins, respectively. For non-traditional CV or disease-related risk factors, 20% still had high disease activity and 65% had elevated sedimentation rate (mean 45.58±18.36 (SD) mm/hr) on latest consult. Eighty seven percent were taking methotrexate but only three percent were on biologic agents.

Conclusion: This study shows the presence of important traditional risk factors such as hypertension, diabetes, dyslipidemia, and obesity in this population. Significantly, more than half the cases have dyslipidemia. In addition, RA disease activity was high to moderate. The combination of traditional and disease related risk factors for cardiovascular disease is ominous and warrants aggressive treatment. In addition, patient education and weight control should be emphasized. It is recommended that this cohort be followed up prospectively.

Keywords: rheumatoid arthritis, cardiovascular risk, filipino patients

Introduction

Rheumatoid arthritis (RA) is a chronic, symmetric, inflammatory, polyarthritis of unknown etiology. It is the most common inflammatory arthritis worldwide and the world prevalence of RA might be around 0.3–1.2%.[1] In the Philippines, the prevalence of rheumatic diseases were reported in surveys through the Community Oriented Programme for the Control of Rheumatic Diseases (COPCORD) initiated by the World Health Organization (WHO) and International League of Association for Rheumatology (ILAR). Prevalence rates for RA were 0.17% for a Filipino urban population[2] and 0.2% for a rural population.[3]

Cardiovascular disease (CVD) remains a major problem for patients with RA. The mortality rate from CVD is increased in RA patients.[4,5,6] RA and many other autoimmune diseases can be considered as a prothrombotic state and a risk factor for venous thromboembolism (VTE) and CVD. Inflammation is probably the link between these illnesses. The inflammatory cytokine network, when activated, induces several prothrombotic conditions such as endothelial

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dysfunction, tissue factor (TF) expression and coagulation activation, inhibition of fibrinolysis and the protein C system.[7] Also, indirectly, there may be a link between adiposity, insulin resistance, inflammation and coagulation, since cytokines like tumour necrosis factor α (TNFα) and interleukin 6 (IL-6) are released in adipose tissue and play a large part in all the above phenomena.[8] Several anticoagulant mechanisms, such as the antithrombin-heparin mechanism, the TF pathway inhibitor (TFPI) mechanism and the protein C anticoagulant system, prevent unwanted clot formation. Evidence shows that these pathways are down regulated by inflammation. Both TFPI and the protein C pathway seem to have a protective effect on endothelial dysfunction and atherosclerosis.[9] Platelets also play an active role in atherothrombosis, and high platelet reactivity is associated with a higher risk of CV events.[10] Several studies have shown an increased platelet count, together with elevated platelet activation markers, like CD62P (P-selectin), CD63 and their subsequent expression in RA.[11]

Cardiovascular (CV) events occur approximately a decade earlier in RA than in the general population,[12] suggesting that RA, similarly to diabetes mellitus, is an independent risk factor for premature ischemic heart disease.[13] The impact of traditional risk factors on the development of cardiovascular disease in persons with RA is an area of active research.[14] These traditional risk factors include: smoking, obesity, hypertension, diabetes mellitus and dyslipidemia. In a study done by Naranjo and colleagues, they found that all traditional CV risk factors, except obesity and physical inactivity, were associated with CV morbidity, and in multivariate models, hypertension, hyperlipidemia, diabetes, and ever-smoking remained independent risk factors.[15] Nontraditional risk factors, like RA disease activity/severity measures, including inflammatory markers, disease activity scores, seropositivity, and corticosteroid use, have repeatedly shown significant associations with increased cardiovascular risk. Van Halm and colleagues[16] found an association between CV disease and seropositive and erosive RA.

Most patients with RA today are treated with a variety of drugs, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease modifying anti-rheumatic drugs (DMARDs) and biologic agents, to relieve symptoms and halt disease progression. NSAIDs are known to increase the risk of hypertension and myocardial infarction. Although there are conflicting results for corticosteroids and thromboembolism, numerous studies have shown unfavorable effects of glucocorticoids on cardiovascular risk and risk factors, such as diabetes, adiposity and blood pressure.[17] Data for CVD or VTE risk and DMARD use in RA are scarce except for methotrexate (MTX) and hydroxycloroquine (HCQ). Meta-analysis and observational studies suggest that MTX and HCQ have beneficial effect, reducing the risk of CVD[18,19] though definitive studies are lacking.

The researchers hypothesize that this study will enlighten us in the presence or absence of important traditional and nontraditional risk factors such as hypertension, diabetes, dyslipidemia, and obesity in this population.

Data from international studies show that cardiovascular risk factors among patients with rheumatoid arthritis are increased. Data from Asian studies, specifically among Filipino patients are few. RA is also a known non-conventional independent risk factor for cardiovascular disease. However, with the racial, ethnic, and lifestyle differences, we would like to evaluate the frequency of the same among our Filipino patients. It is important to evaluate this in our population to foster a more holistic approach to monitoring and treatment. This research will also serve as a baseline database for patients with CV risk factors for future studies on the impact of RA on cardiovascular morbidity and mortality.

The researchers aim to describe the presence of cardiovascular risk factors among filipino patients with rheumatoid arthritis seen in the Philippine General Hospital Rheumatology outpatient department. More specifically;

1. To identify the prevalence of traditional cardiovascular risk factors among Filipino patients with RA, including:
   a. Smoking
   b. Obesity
   c. Hypertension
   d. Diabetes mellitus or impaired fasting glucose (IFG)
   e. Dyslipidemia-hypercholesterolemia, hypertriglyceridemia, hyperlipidemia (LDL), decrease in high density lipoproteins (HDL)
2. To identify the presence of nontraditional cardiovascular risk factors among patients with RA, particularly:
   a. Disease activity using the Disease Activity Score (DAS-28)
   b. Inflammatory marker (erythrocyte sedimentation rate)
   c. Seropositivity (rheumatoid factor)
3. To identify the prevalence of use of anti-inflammatory disease-modifying agents and medications targeting traditional CV risk factors (e.g., statins, anti-hypertensives, hypoglycemic agents).

Methods

The design used in the study is retrospective Patients diagnosed with rheumatoid arthritis by the 1987 American College of Rheumatology (ACR)[20] or 2010 ACR-EULAR classification criteria for rheumatoid arthritis[21] included in the RADAR being seen at the Philippine General Hospital (PGH) Rheumatology OPD Clinic were involved in the study. On the other hand, patients diagnosed with rheumatoid arthritis, who do not fulfill the 1987 and/or the 2010 ACR criteria for RA were excluded.

The sampling procedure utilized in the study is non-probability sampling. Clinical case records of patients diagnosed with RA included in the RADAR were reviewed. Data extracted were analyzed according to the following

clinical aspects: demographics (gender, age at onset of RA; disease duration, employment status); pertinent data from history and physical examination (past medical, personal and social history, body mass index, RA disease activity scores); ancillary procedure results including acute phase reactant levels, lipid profile, electrocardiogram and chest roentgenogram readings; and use of steroids, NSAIDs, disease modifying anti-rheumatic drugs and cardiovascular agents over the course of illness. Statistical analyses used was descriptive statistics including frequency tables

Operational definitions

A. Hypertension according to the Eight Report of the Joint National Committee on the Prevention, Detection, and Treatment of High Blood Pressure (JNC 8)[22] is an average measured systolic blood pressure greater than or equal to 140 mmHg and/or an average measured diastolic blood pressure greater than or equal to 90 mmHg after two or more seated BP readings.

B. Dyslipidemia is defined as presence of any of the following[23]:

1. High density lipoprotein (HDL) < 40 mg/Dl
2. Low density lipoprotein (LDL) > 130 mg/Dl
3. Total cholesterol (TC) > 200 mg/dL, or/and
4. Total triglycerides (TG) > 200 mg/dL

C. The World Health Organization, the International Obesity Task Force, and the International Association for the Study of Obesity have proposed lower cut-off points for overweight (body mass index (BMI)=23.0 kg/m^2) and obesity (BMI=25.0 kg/m^2) in asian and pacific island populations.[24]

D. Disease Activity Score (DAS-28) - This criterion was developed to assess patients with rheumatoid arthritis. It consists of 28 areas to assess for joint tenderness and swelling together with ESR and visual analog score (VAS), calculated using automated DAS 28 calculator. For the purpose of this study, the score 2.6 and below was grouped as remission, <3.2 as low disease activity, 3.2-5.1 as moderate and the score >5.1 will be grouped as high disease activity index.

All patient information were anonymized and kept confidential. This research was submitted to the UPM Research Ethics Board (UPMREB) PGH Panel for review and approval granted. There are no conflicts of interest for this study.

Results

The authors included ninety eight patients from the Rheumatoid Arthritis Database and Registry (RADAR). There was a female predominance of 15:1. Mean age at diagnosis of rheumatoid arthritis was 49.95±10.17 (SD) years and mean age of onset of symptoms was 45.51±10.89 (SD) years. Disease duration prior to diagnosis was 41.79 months while mean disease duration from diagnosis to latest follow-up was 63.01 months. (Table I)

Table I. Demographic data of 98 patients with rheumatoid arthritis included in this study

	Frequency (%)
Gender	
Male	6 (6)
Female	92 (94)
Employment (n=66)	
Never	14 (21)
Previous	35 (53)
Current	17 (26)
Family History	
Hypertension/CV disease	47 (48)
Diabetes mellitus	21 (21)
Rheumatoid arthritis	4 (4)

Table II. Traditional cardiovascular risk factors present in included patients (n=98)

Traditional CV factors	Frequency (%)
Hypertension	38 (39)
Diabetes mellitus/impaired fasting glucose	19 (19)
Smoking	18 (18)
BMI (mean)	23.85 ± 4.60 (SD)
Overweight (n=71)	16 (23)
Obese (n=71)	24 (34)
Dyslipidemia	
Hyperlipidemia (↑LDL) (n=93)	31 (33)
Hypertriglyceridemia (n=93)	5 (6)
Decreased HDL (n= 93)	20 (22)
Hypercholesterolemia (n=96)	38 (40)

Table III. Disease characteristics/non-traditional cardiovascular risk factors of included patients

Disease related risk factors	Earliest documented	On latest consult
DAS 28 scores (mean)	5.0 ± 1.41 (SD)	3.82 ± 1.09 (SD)
ESR (mean)	45.95 ± 16.42 (SD)	45.58 ± 18.36 (SD)
		On latest consult Frequency (%)
DAS 28 (n=54)		
Remission	-	6 (11)
Low	-	10 (19)
Moderate	-	27 (50)
High	-	11 (20)
RF positive (n=85)	-	61 (72)

Traditional CV risk factors are seen in Table II. Thirty four percent (24 of 71, with available data) were obese and 23% (16 of 71) were overweight. Mean BMI was 23.85±4.31 (SD) kg/m^2. Eighteen percent were smokers. For the co-morbidities, 39% have hypertension, 19% had impaired fasting glucose (IFG) or diabetes mellitus (DM), and 55% have dyslipidemia.

Non-traditional cardiovascular risk factors are seen in Table III. On latest consult 50% and 20% still had moderate and high disease activity, respectively. Mean disease activity score using DAS 28 on latest consult was 3.81±1.09 (SD) with 65% having elevated ESR, with a mean of 45.58 mm/hr. Seventy two percent were rheumatoid factor (RF) positive.

Only 34 patients had electrocardiograms (27 were normal, one has left atrial enlargement and six had nonspecific changes). Eleven percent had atherosclerotic aorta and eight perrcent of had cardiomegaly on chest

Table IV. Medications received by the patients included in the study

Medications	Frequency (%)
Pain killers:	
NSAIDs	88 (90)
Paracetamol	9 (9)
Opiates	3 (3)
Steroids	76 (78)
RA medications	
Methotrexate	85 (87)
Other synthetic DMARDs	34 (35)
Biologic DMARDs	3 (3)
Medications for concomitant conditions	
Anti-Hypertensive agents (n=38 pxs with HTN)	33 (87)
Anti-lipidemics (n=54 pxs with dyslipidemia)	18 (33)
Hypoglycemic agents (n=19 pxs with IFG or DM)	10 (53)

radiograph. With regards to anti-inflammatory disease-modifying agents (Table IV), 86% were on methotrexate but only three percent were on biologics. Eighty seven percent of patients with hypertension were on anti-hypertensive medications, only 53% of those who had IFG or diabetes and only 33% of those with dyslipidemia were taking oral hypoglycemic agents and statins, respectively.

This study proved our hypothesis with regards to the presence of important traditional risk factors such as hypertension, diabetes, dyslipidemia, and obesity in this population. Significantly, more than half the cases have dyslipidemia. In addition, RA disease activity was high to moderate. The combination of traditional and disease related risk factors for cardiovascular disease is ominous and warrants aggressive treatment.

Discussion

Rheumatoid arthritis (RA) is a chronic, multisystem autoimmune disease of unknown etiology that most frequently appears between the fourth and fifth decades of life.[25] The mean age at RA diagnosis in our patients approximates international data where in the incidence increases with age during adulthood, except among men age 40 to 60.[26] This is also around the same time CV disease frequently manifests. Patients with RA have higher odds of having traditional CV risk factors including smoking, obesity, hypertension, diabetes mellitus and dyslipidemia. In a study done by Naranjo and colleagues, they found that all traditional CV risk factors, except obesity and physical inactivity, were associated with CV morbidity, and in multivariate models, hypertension, hyperlipidemia, diabetes, and ever-smoking remained independent risk factors.[15] The prevalence of hypertension and DM (39% and 19%, respectively) among patients with RA included in our study were much higher than the reported local prevalence of these illnesses in the Philippines based on the National Nutrition and Health Survey (NNHeS)[27] (17.4% and 3.4%, respectively). International data shows lifestyle factors such as smoking and obesity are also higher in patients with RA.[28] This is comparable to the higher prevalence of smokers in our cohort (18%) compared to that in the general population (12.1%).[29] Patients who are disabled by their arthritis are more likely to be overweight or obese[30] itself a risk factor for metabolic syndrome and CVD.[31] Furthermore, overweight patients with RA tend to have worse disease activity[32] contributing to the systemic inflammatory responses that lead to accelerated atherosclerosis. In our study, more than half of our patients are either overweight or obese. Our cohort of patients also showed cardiovascular related changes on chest radiograph, 11% had atherosclerotic aorta and eight percent had cardiomegaly.

The increased CVD morbidity and mortality seen in RA cannot be entirely explained by an increase in traditional risk factors.[33] Disease-specific CV risk factors, on the other hand, are direct consequences of chronic inflammation and include elevated acute phase reactants like ESR. Majority of our patients still have elevated ESR at their latest consult, although the values were decreased from baseline evaluation suggesting some control from medications. These may predispose to an increased risk of myocardial infarction and related mortality. Furthermore, 72% of our patients have positive RF and the presence of such autoantibodies is associated with an increased CVD risk in RA[34] and in the general population[35] possibly by direct endothelial injury.

Aside from the need to encourage patients to aggressively correct their modifiable risk factors, the presence of these CV comorbidities has important implication in the therapy of patients with RA. There is evidence that methotrexate, considered a mainstay of therapy for RA, can ameliorate some of this excess CVD risk through reducing systemic inflammation and by directly affecting some of the cellular mechanisms that lead to atherosclerosis.[36] Majority of our patients are on methotrexate (87%) but in most of them we have not reached our target of low disease activity or remission. Advances in our understanding of the key cells and inflammatory cytokines have led to the development of targeted biologic agents. As of 2011, 5 TNF-alpha inhibitors are approved for use by the FDA: infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol. In randomized clinical trials, all of these agents have been shown to be effective in reducing clinical signs of inflammation in RA patients who have failed synthetic DMARDs.[37] Unfortunately, in our cohort of patients, only three percent of them are receiving biologic agents which could explain why still have a lot of patients with moderate to high disease activity scores.

Conclusion and Recommendation

This study shows the presence of important traditional risk factors such as hypertension, diabetes, dyslipidemia, and obesity in this population. Significantly, more than half the cases have dyslipidemia. In addition, RA disease activity was high to moderate. The combination of traditional and disease related risk factors for cardiovascular disease is ominous and warrants aggressive treatment. In

addition, patient education and weight control should be emphasized. It is recommended that this cohort be followed up prospectively.

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