Associations between Depression and Carotid Artery Intimal Thickness in patients with Rheumatoid Arthritis

Ying Liu, PGY1

Study Purpose and Rationale

Although RA is associated with pain and morbidity, RA patients also have high rates of cardiovascular disease (CVD)[1], and it is a significant cause of mortality.[2] This is thought to be mediated through inflammation, as RA is a highly inflammatory state.[3] RA patients also have a higher prevalence of psychosocial morbidities and these cause significant burden both to quality of life/disease severity and healthcare costs.[4,5] Rates of depression are especially high, and multiple studies have estimated the prevalence of depression in RA patients to be about 15%,[6,7]as compared to 6.6% in the general population.[8] Psychosocial comorbidities, such as depression, are also associated with risk for CVD.[9,10] This is also thought to be mediated through inflammation.[11,12] Interestingly, RA patients are often younger and lack traditional risk factors associated with CVD.[13] Some studies have found that RA patients have a high burden of atherosclerosis in the carotids, and Carotid thickness is a good predictor of CVD risk in RA patients.[14,15] However, the association between psychosocial comorbidities and CVD in RA patients is still unclear, and few studies have investigated the role of psychosocial comorbidities as additional cardiac risk factors in RA patients

Questions:

- Is depression more common in RA patients?
- Is depression associated with internal carotid artery (ICA) and common carotid artery (CCA) intimal thickness?
- Does this association vary between patients with RA and controls? If so, is the interaction significant?

Hypothesis:

Depression will be more common in RA patient, and it will be associated with increased carotid artery thickness, with a larger effect in RA patients.

Study Design and Statistical Analysis

This is a cross-sectional analysis of the association between depression and carotid artery thickness (ICA and CCA) in patients with RA as compared to controls without RA derived from the MESA (Multi-Ethnic Study of Atherosclerosis) cohort.

ESCAPE RA (Evaluation of Subclinical Cardiovascular disease And Predictors of Events in Rheumatoid Arthritis) is a cohort study of the prevalence, progression, and risk factors for subclinical CVD in men and women with RA.[16] It was designed with identical inclusion and exclusion criteria (except for the diagnosis of RA) to those of the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based cohort study of subclinical CVD with similar objectives. One-hundred ninety-five RA participants were recruited from the Johns Hopkins Arthritis Clinic and by referral from local rheumatologists from October 2004 through May 2006. Informed consent was obtained from all participants, and the study was approved by the Institutional Review Board of the Johns Hopkins Hospital.

The controls without RA were selected from MESA participants enrolled in the Baltimore Field Center. Frequency matching was used to select a control group with similar demographic characteristics as the

RA group, using sixteen substrata defined by gender (male/female), age (9 year increments), and race (black/white). A description of MESA design and methods has been published previously.[17] In brief, MESA enrolled a multiethnic cohort of 6,814 participants aged 45-84 years without clinically apparent CV disease from six U.S. communities between 2000 and 2002, among whom 1,086 were enrolled by the Johns Hopkins (Baltimore) Field Center. MESA participants who reported use of disease-modifying anti-rheumatic drugs (DMARDs) that are typically used for the treatment of RA were excluded as potential controls. A total of one hundred ninety-eight MESA controls were available for the analyses.

Sample Size Calculations

In a previous study, investigators found ICA thickness in the RA population to range from 1.15-1.16mm and in the control study from 1.02-1.04mm, leading to differences in ICA thickness of 0.11-0.14 mm between patient with and without RA. Assuming that depression may have a smaller effect size and smaller difference, we assumed an effect size of 0.1mm. Previously estimated SD was about 0.1mm.

In addition, the CDC estimates the prevalence of depression in U.S. adults is about 6.6%. Prior studies have found an elevated prevalence of depression in the RA population, and many studies have estimated a prevalence of 15%.

We calculated sample size using a two-group t-test of means formula. We set our alpha to be 0.05 and power to be 0.80.

For the RA population, we expect unequal group sizes for those with and without depression (1:6) based on our depression prevalence estimate of 15%. Using a group 1 (depression) mean of 1.15 and group 2 (not depressed) mean of 1.05 and standard deviation of 0.1 with group2/group1 ratio of 6, the necessary sample size for the depressed group is 11 and for the non-depressed group is 66. We meet this requirement as we have 195 patients with RA and expect 29 to be in the depressed group and 166 to be in the non-depressed group.

For the control population, we expect unequal group sizes for those with and without depression (1:13) based on our depression prevalence estimate of 6.6%. Using a group 1 (depression) mean of 1.15 and group 2 (not depressed) mean of 1.05 and standard deviation of 0.1 with group2/group1 ratio of 13, the necessary sample size for the depressed group is 11 and for the non-depressed group is 135. We meet this requirement as we have 198 controls and expect 13 to be in the depressed group and 178 to be in the non-depressed group.

Given the above parameters and sample sizes, we can detect an effect size as small as 0.056mm in our RA patients and 0.081mm in our controls.

Analysis Plan:

- Examine various demographic variables and health measures by RA for whole cohort (RA patients plus MESA controls)
    - Assess for normality and distribution of variables
    - Look for significant differences in covariates between patients with and without RA
- Examine the depression variable (univariate analysis) looking at normality and distribution
    - Explore any correlations between the different variables
    - Based on distribution, may make a categorical variable using recommended cutoff of 16 for clinical depression

- Examine the outcome variable of ICA and CCA intimal thickness
    - Assess for normality and logarithmically transform
- Examine associations between depression and RA status, both unadjusted (t-tests/ranksum and chi-squared) and then adjusted for covariates from table I (linear and log regression)
- Examine associations between depression and carotid artery intimal thickness (ICA and CCA)using scatterplots and then linear and log regression, unadjusted and then adjusted with covariates
    - Explore the effect of adding RA into the above models and explore any effect modification (interaction terms)

Study Procedure

Overview:

During an initial visit patients completed a questionnaire evaluating demographic variables and other health variables including chronic diseases, medications, and activity level. RA patients also answered questions about disease activity and RA-specific therapies. Blood was drawn to collect data on lipids, glucose and inflammatory markers. Finally, the patients were referred for ultrasound of the head and neck to assess ICA and CCA intimal thickness at MESA centers using standard protocols.

Depression Assessment – Centers for Epidemiological Studies Depression Scale (CES-D)

The CES-D is a well-validated scale with high internal consistency (Cronbach's alpha coefficient of 0.85 in the general population and 0.90 in psychiatric patients), that has also been found to correlate well with other scales, symptoms, and life events. The scale consists of 20 items that are scored by summation of responses (0=rarely, 1=some of the time, 2=occasionally or moderately, 3=most or all the time) with a range of 0-60. Questions 4 (You felt that you were just as good as other people), 8 (You felt hopeful about the future), 12 (You were happy), and 16 (You enjoyed life) were reverse-scored according to guidelines.[18] Scores ranged from 0-60. If any missing data existed for one question, the total score was not calculated.

Carotid Imaging

Ultrasound imaging of the carotid arteries was performed in ESCAPE-RA participants using MESA ultrasound procedures, technicians and equipment (Logiq 700, General Electric Medical Systems). The probe frequency utilized for the ICA/bulb was 9 MHz; for the CCA was 13 MHz; and for the pulsed Doppler studies was 4.0 MHz. The imaging protocol involved obtaining a single longitudinal lateral view of the distal 10 mm of the right and left CCA and three longitudinal views in different imaging planes of each BULB-ICA. The BULB-ICA was defined as including both the carotid bulb, identified by the loss of parallel wall present in the CCA, and the 10 mm segment of the ICA distal to the tip of the flow divider that separates the external and internal carotid arteries.

Videotaped scans were analyzed at the MESA Ultrasound Reading Center. The baseline carotid scans of the MESA controls served as the comparator scans, and these were re-analyzed at the same time as the ESCAPE-RA scans by a single MESA reader blinded to RA status. Maximal IMT was measured in end diastole at each of the near and far walls of the right and left CCA, and the anterior oblique, lateral and posterior oblique views of the BULB-ICA, for a total of 16 IMT measurements per person. The mean maximal IMTs of the CCA and BULB-ICA were obtained by averaging the maximal measurements from the near and far walls at each projection, from the right and left sides. For internal carotid IMT measurements, intraobserver coefficient of variation was 6.93%, and interobserver coefficient of variation was 18.8%. For common carotid IMT measurements, intraobserver and interobserver coefficients of variation were 3.48% and 10.7%, respectively.[19]

Study Drugs – NONE

Medical Device – NONE

Study Questionnaires – Based on MESA standardized questionnaires with additional questionnaires on RA activity developed for the ESCAPE-RA trial (http://www.nhlbi.nih.gov/resources/obesity/pop-studies/mesa.htm)

Study Subjects/Recruitment
ESCAPE RA inclusion criteria were:
(1) fulfillment of American College of Rheumatology criteria for the classification of RA (25) of > 6 months; and
(2) ages 45-84 years.

ESCAPE RA Exclusion criteria were:
(1) prior self-reported physician-diagnosed myocardial infarction (MI), heart failure, coronary artery revascularization, peripheral vascular (arterial) disease or procedures, implanted pacemaker or defibrillator devices, and current atrial fibrillation,
(2) weight exceeding 300 pounds (due to imaging equipment limitations), and
(3) CT scan of the chest within six months prior to enrollment (to limit radiation exposure).

Confidentiality of Study Data
The data is stored with the study coordinator under lock and key according to MESA protocols. All analysis was done using de-identified data using study-specific ID numbers.

Conflicts of Interests – none

Location of Study
The recruitment and data collection for this study was all done at Johns Hopkins University Medical Center. All data were gathered and all labs were processed according to MESA protocols.

Potential Risks
There are no additional potential risks to patients as this study only requires routine visits, a few extra blood draws, and ultrasound of the head and neck for carotid thickness measurements, which are all relatively benign procedures that add little extra risk.

Potential Benefits
These patients will receive extra assessments (labs, ultrasound…etc.) for free that can help their overall medical care. They will also be screened for depression and stress that could be treated or ameliorated.

Alternative Therapies
None

Compensation to Subjects - None

Costs to Subjects
Travel for extra visits and time for assessments

Minors as Research Subjects – None

Radiation or Radioactive Substances – None

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