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Original Article

Clinical assessment of endothelial function in patients with rheumatoid arthritis: A meta-analysis of literature studies

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ABSTRACT

Background: Several studies reported an increased cardiovascular (CV) morbidity and mortality in patients with rheumatoid arthritis (RA). Flow-mediated (FMD) and nitrate-mediated dilation (NMD) are considered non-invasive methods to assess endothelial function and surrogate markers of subclinical atherosclerosis.
Methods: We performed a systematic review with meta-analysis and meta-regression of literature studies evaluating the impact of RA on FMD and NMD. Studies evaluating the relationship between RA and markers of CV risk (FMD and NMD) were systematically searched in the PubMed, Web of Science, Scopus and EMBASE databases. The random-effect method was used for analyses and results were expressed as mean difference (MD).
Results: A total of 20 studies (852 RA patients, 836 controls) were included in the final analysis. In detail, 20 studies with data on FMD (852 cases, 836 controls) and 5 studies with data on NMD (207 cases, 147 controls) were analyzed. Compared to controls, RA patients showed a significantly lower FMD (MD: −2.16%; 95% CI: −3.33, −0.98; P = 0.0003), with no differences in NMD (MD: −0.41%; 95% CI: −2.89, 2.06; P = 0.74). Interestingly, a lower FMD (MD: −2.00%; 95% CI: −3.20, −0.80; P = 0.001) and no differences in NMD (P = 0.49) were confirmed when excluding data on patients with early-RA. Meta-regression models showed that a more severe inflammatory status was associated with a more significant impairment in FMD.
Conclusions: RA patients show impaired FMD, which is currently considered an independent predictor of CV events. The presence of endothelial dysfunction in RA should be taken into account to plan adequate prevention strategies and therapeutic approaches.

1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disorder that affects synovial joints and leads to chronic pain, bone erosions and progressive disability [1]. With a prevalence of 0.5–1% in the general population, RA is the most common chronic inflammatory condition [2, 3].

Beyond joint disease, RA is characterized by a high prevalence of comorbidities, such as gastrointestinal [4, 5], respiratory [6, 7], and renal diseases [5, 8]. Moreover, metabolic syndrome (MetS) and its major features (obesity, hypertension, impaired fasting glucose, hyperlipidemia) have been frequently found in RA patients [9]. RA is also associated with shortened life expectancy [1], cardiovascular (CV) disease accounting for 35–50% of excess mortality in this clinical setting [10]. Accordingly, death for ischemic heart disease and cerebrovascular accidents is significantly higher in RA than in the general population [11].

The increased CV morbidity and mortality in patients with RA cannot be entirely explained by traditional CV risk factors and the mechanisms leading to the increased CV risk in RA are not yet clearly understood [12, 13]. Thus, the association between RA and subclinical atherosclerosis, a recognized marker of cardiovascular (CV) disease [14], is still a matter of study.

Endothelial dysfunction is the earliest stage of the atherosclerotic process and even a trigger of CV events [15]. Flow-mediated dilation (FMD) and nitrate-mediated dilation (NMD) are widely accepted as accurate and non-invasive methods to assess endothelial function in humans [16] and, in turn, as surrogate markers of subclinical atherosclerosis [17]. Moreover, FMD is currently considered an independent predictor of CV events [18], thus providing important prognostic data over and above traditional CV risk factors.

During recent years, there has been growing interest in the relationship between these markers of CV risk and RA. In particular, some case–control studies reported impaired endothelial function in RA patients [15, 19]. However, these data have been challenged in recent studies [20, 21] and no meta-analytical data providing an overall information about this issue are currently available.

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The aim of the present study is to perform a systematic review and meta-analysis of all studies evaluating the impact of RA on FMD and NMD. Moreover, we implemented some meta-regression models to evaluate the effect of some clinical and demographic variables on these outcomes.

2. Methods

A protocol for this review was prospectively developed, detailing the specific objectives, the criteria for study selection, the approach to assess study quality, the outcomes, and the statistical methods.

2.1. Search strategy

To identify all available studies, a detailed search pertaining to RA and the markers of CV risk (i.e. FMD and NMD) was conducted according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines [22]. A systematic search was performed in the electronic databases (PubMed, Web of Science, Scopus, EMBASE), using the following search terms in all possible combinations: rheumatoid arthritis, flow-mediated dilation, nitrate-mediated dilation, endothelium-dependent dilation, endothelium-independent dilation, endothelial function, endothelial dysfunction. The last search was performed on 5th April 2015. The search strategy was developed without any language restriction.

In addition, the reference lists of all retrieved articles were manually reviewed. In case of missing data, study authors were contacted by e-mail to try to retrieve original data. Two independent authors (MNDDM and PA) analyzed each article and performed the data extraction independently. In case of disagreement, a third investigator was consulted (RL). Discrepancies were resolved by consensus. Selection results showed a high inter-reader agreement ($\kappa = 1$) and have been reported according to PRISMA flowchart (Appendix 1).

2.2. Data extraction and quality assessment

According to the pre-specified protocol, all studies evaluating the impact of RA on the markers of CV risk were included. Case-reports, case-series without a control group, reviews and animal studies were excluded. To be included in the analysis, a study had to provide values (means with standard deviation or standard error) of brachial artery FMD and/or NMD among RA patients and controls. The included studies were classified as having a case–control design or a cohort design.

In each study, data regarding sample size, major clinical and demographic variables, values of FMD and NMD in RA patients and controls were extracted.

Given the characteristics of the included studies, the evaluation of methodological quality of each study was performed with the Newcastle-Ottawa Scale (NOS), which is specifically developed to assess quality of non-randomized observational studies [23]. The scoring system encompasses three major domains (selection, comparability, exposure) and a resulting score range between 0 and 8, a higher score representing a better methodological quality. Results of the NOS quality assessment are reported in Appendix 2.

2.3. Statistical analysis and risk of bias assessment

Statistical analysis was carried out using Review Manager [Version 5.2, The Cochrane Collaboration, Copenhagen, Denmark] provided by The Cochrane Collaboration.

Differences among cases and controls were expressed as mean difference (MD) with pertinent 95% confidence intervals (95% CI). A different variance of the estimator among studies has been assumed for the analyses.

Endothelial function has been expressed as the percentage change (%) in the brachial artery diameter from baseline to maximal dilation during reactive hyperemia (FMD) or after sublingual nitrate administration (NMD).

The overall effect was tested using Z-scores and significance was set at $P < 0.05$. In order to be as conservative as possible, the random-effect method was used for all analyses to take into account the variability among included studies. Statistical heterogeneity between studies was assessed with chi square Cochran's Q test and with I^2 statistic, which measures the inconsistency across study results and describes the proportion of total variation in study estimates, that is due to heterogeneity rather than sampling error. In detail, I^2 values of 0% indicate no heterogeneity, 25% low, 25–50% moderate, and 50% high heterogeneity [24].

Publication bias was represented graphically by funnel plots of the effect size (mean difference) versus precision (1/standard error of the mean difference) for studies evaluating flow-mediated dilation and nitrate-mediated dilation in patients with rheumatoid arthritis and in control subjects using both fixed and random effects. Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect, and Egger's and Begg and Mazumdar tests were used to assess publication bias, over and above any subjective evaluation. A $P < 0.10$ was considered statistically significant [25]. Moreover, the Duval and Tweedie's trim and fill analysis was used to allow for the estimation of an adjusted effect size after trimming and imputing studies [26].

2.4. Sensitivity analyses

We repeated sensitivity analyses by including only the studies judged as “high quality” according to NOS (i.e. NOS ≥ the median value found among included studies).

In order to avoid the risk of data overlap, a sensitivity analysis was performed after excluding studies involving the same recruitment Centres and enrolling patients in the same period time as other included studies.

To overcome the potential impact of CV risk on FMD and NMD, a further sensitivity analysis was performed by analyzing only studies specifically including RA patients and matched controls without traditional CV risk factors.

2.5. Subgroup analyses

Given the potential influence of disease duration on the outcomes, we planned to perform separate analyses for studies on early-RA (defined by a disease duration <12 months) and late-RA (defined by a disease duration ≥12 months).

2.6. Meta regression analyses

We hypothesized that differences among included studies may be affected by demographic variables (mean age, male gender) and clinical data related to disease activity [disease activity score in 28 joints (DAS28), rheumatoid factor (RF) positivity, C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), disease duration], antirheumatic treatment [therapy with methotrexate (MTX)], and coexistence of traditional CV risk factors (hypertension, smoking habit, diabetes mellitus, obesity, hyperlipidemia). To assess the possible effect of all these variables in explaining different results observed across studies, we planned to perform meta-regression analyses after implementing a regression model with changes in FMD or NMD as dependent variables (y) and the above mentioned covariates as independent variables (x). This analysis was performed with Comprehensive Meta-analysis [Version 2, Biostat, Englewood NJ (2005)].

3. Results

After excluding duplicate results, the search retrieved 101 articles. Of these studies, 51 were excluded because they were off the topic after

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