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Clinical relevance of antiphospholipid antibodies in systemic sclerosis: A systematic review and meta-analysis☆

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ABSTRACT

Objective: To evaluate the clinical relevance of antiphospholipid antibodies (aPL) in systemic sclerosis (SSc).

Methods: A systematic search of EMBASE and PubMed databases from January 1983 to July 2016 was carried out according to PRISMA guidelines whereas Peto's odds ratio (OR) for rare events was used for the meta-analysis.

Results: The pooled prevalence of participants positive for IgG and IgM anticardiolipin (aCL) antibodies was higher in SSc than controls (12.8% vs 1.6% and 7.8% vs 0.6%; $p < 0.0001$ for both) as was that of IgG and IgM anti-beta-2-glycoprotein-I antibodies (aβ_2GPI) (6.1% vs 0.58%, $p < 0.0001$; 3.5% vs 0.3%, $p = 0.001$). The pooled prevalence of pulmonary arterial hypertension (PAH) was more common in SSc positive than negative patients for aCL (IgG/IgM combined) (26.5% vs 10.9%, $p < 0.0001$) whereas the pooled prevalence of renal disease (RD) was more common in IgG aCL positive than negative patients (36.3% vs 10.9%, $p = 0.02$). The pooled prevalence of thrombosis was higher in IgG aCL, IgM aCL, and IgM aβ_2GPI positive than negative SSc patients (12.6% vs 1.4%, $p < 0.0001$), (15.1% vs 2.7%, $p = 0.002$) and (15% vs 0.78%, $p = 0.009$), respectively. The pooled prevalence of digital infarction/ischemia (DI) was higher in IgG aCL and IgM positive than negative SSc (52.8% vs 39.8%, $p = 0.002$) and (68.1% vs 29%, $p = 0.07$).

Conclusions: A strong relationship exists between aCL and aβ_2GPI of IgG/IgM isotype and SSc; patients positive for these antibodies are more likely to suffer from PAH, RD, thrombosis, and DI. However, data expressed as frequency of aPL positive patients rather than average antibody titers preclude further insight into the relevance of these assumptions.

Introduction

Systemic sclerosis (SSc) is characterized by endothelial damage that over time develops into micro- and macro-vascular disease followed by the appearance of clinical symptoms involving the skin, lungs, kidneys, heart, and gastrointestinal tract. Digital infarction/ischemia (DI), acute and chronic renal disease (RD), and pulmonary arterial hypertension (PAH) are some typical manifestations of long standing endothelial damage [1]. The first reports of arterial [2,3] and venous occlusions [4] in patients with SSc appeared in the early 70s, occasionally associated with the presence of antiphospholipid antibodies (aPL) [5,6]. Ever since, several investigators addressed the potential role of aPL in SSc with regards to thrombosis and to other vascular manifestations of SSc. The purpose of this systematic review and meta-analysis is to assess the available evidence for a possible or definitive role of aPL in SSc.

Material and methods

Search strategy and selection criteria

A systematic review according to the PRISMA guidelines [7] was carried out by searching the electronic databases MEDLINE and EMBASE from January 1983 to July 2016. For the search strategy we used the terms [“systemic sclerosis” OR “scleroderma”] and [“anticardiolipin” OR “anti-beta 2-glycoprotein-I” OR “antiphospholipid syndrome,” OR “lupus anticoagulant” OR “lupus inhibitor”]. The search yielded 1093 records that were processed according to Figure 1.

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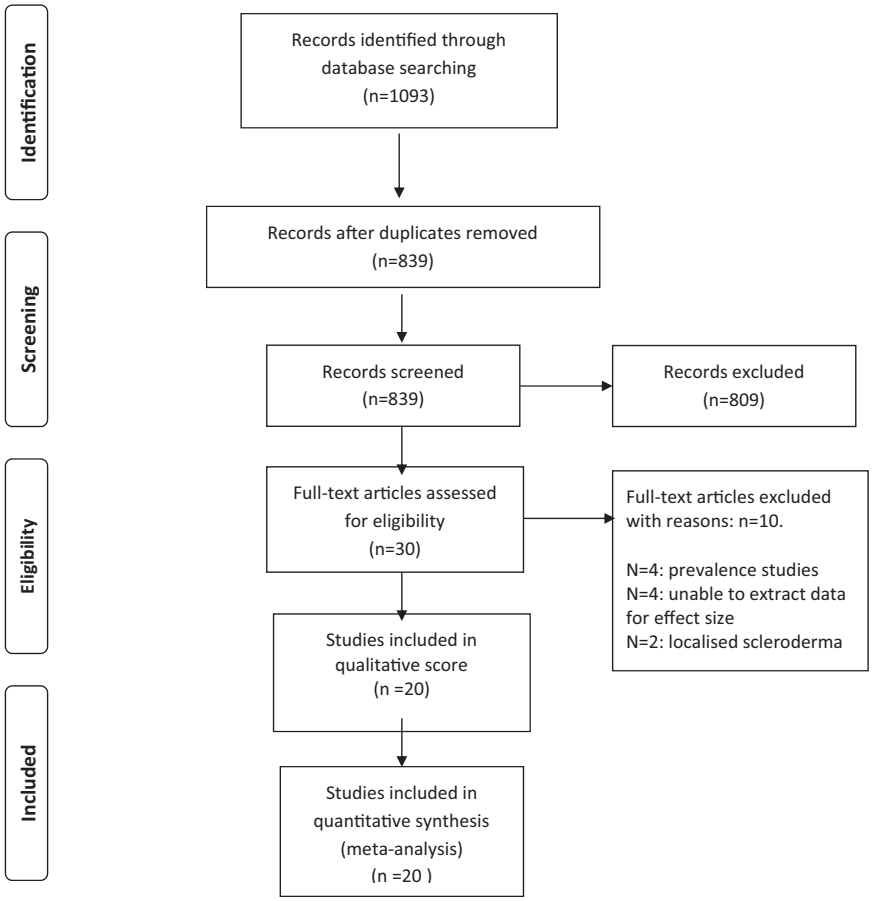

Fig. 1. Summary of literature search according to the Prisma flow-chart.

Criteria for selecting articles

Two investigators (M.M. and P.R.J.A.) screened all the retrieved articles for relevancy. Inclusion criteria were as follows: (1) observational studies (case–control, cross-sectional or cohort) investigating (a) the difference in aPL prevalence and titer between SSc and controls, (b) the difference in aPL prevalence and titer between different vascular manifestations of SSc, and (c) the difference in the prevalence of vascular manifestations between SSc patients positive and negative for aPL; (2) aPL measured by immune or clotting assays; and (3) articles written in English, French, Spanish, German, or Portuguese. If more than two studies investigated the same population, the latest or highest-quality study was chosen. Exclusion criteria were as follows: (1) prevalence studies only; (2) non-original research; (3) studies not reporting the relationship between aPL and SSc; and (4) articles not written in the languages indicated in the inclusion criteria. M.M. and P.R.J.A. applied the eligibility criteria to identify appropriate studies for inclusion and independently extracted data including date of publication, study design, populations, participant data, and results.

Evaluation of the quality of the studies

The quality of the studies identified was assessed by the Newcastle–Ottawa Quality Assessment Scale (NOQAS) for case–control studies specifically developed to assess quality of observational studies; the case–control studies included in the meta-analysis are simply comparing two different groups because they had no real exposure to qualify as true case–control and the same applies to the SSc cohorts with or without certain clinical manifestations or with or without aPL [8]. The scale covers three major domains (selection of cases and controls, comparability of selected groups, and ascertainment of either the exposure or outcome of interest) and the resulting score may range between 0 and 8, a higher score representing a better methodological quality. Data were independently extracted into a standard electronic form and averaged and any discrepancies were resolved by consensus.

Outcome measures

The primary outcomes were as follows: (1) the comparative pooled prevalence of participants positive for aPL in SSC and controls (with odd ratios and level of significance); (2) the standardized mean difference of aPL titers between SSc and controls; and (3) the comparative pooled prevalence of aPL in MS participants with and without several vascular manifestations of SSc, alternatively the pooled prevalence of several vascular manifestations in SSc patients with and without aPL. Secondary outcomes were as follows: (1) the pooled standardized mean differences of aPL titer measured in SSc patients and controls and (2) the pooled standardized mean differences of aPL titer measured in SSc patients with and without a defined clinical manifestation.

Statistical analysis

Statistical analysis was carried out using Comprehensive Meta-Analysis, Biostat, USA; Peto's method for pooled odds ratios was used to compare aPL in SSc and control groups because it is the appropriate statistical analytic method for rare