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Subclinical atherosclerosis in Behcet's disease: A systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate subclinical atherosclerosis in Behcet disease (BD), we performed a systematic review and meta-analysis of studies where atherosclerosis was determined by flow-mediated dilatation (FMD) and endothelial-mediated dilatation (EMD) and by measurement of intima media thickness (IMT) of carotid arteries.

Methods: Systematic search of EMBASE and PubMed databases from January 2000 to January 2014 according to PRISMA guidelines.

Results: Nine studies met the inclusion criteria on FMD/EMD, 11 on IMT and 4 on both. BD had lower FMD than controls (SMD = −0.89, 95% CI: −0.660 to −1.11, $p < 0.001$), which was confirmed by subgroup analyses on active and inactive patients (SMD = −1.17, 95% CI: −1.45 to −0.89 and SMD = −0.72, 95% CI: −0.97 to −0.46, $p = 0.0001$ for both). EMD was lower in BD but with a large estimate (SMD = 0.38, 95% CI: −0.79 to −0.03, $p = 0.06$, $I^2 = 82.2\%$). IMT was greater in BD and the large estimate (SMD = 0.95, 95% CI: 0.63–1.28, $p < 0.0001$, $I^2 = 87.6\%$) persisted after subgroup analysis on active and inactive patients ($I^2 = 88.4\%$ and 86.7%, respectively). Pooling IMT studies by a Newcastle Ottawa Scale of 5 and 6/7 yielded lower estimates (SMD = 0.54, 95% CI: 0.32–0.75, $p < 0.0001$, $I^2 = 58.7\%$ and SMD = 1.72, 95% CI: 1.35–2.09 $p < 0.05$, $I^2 = 48.6\%$).

Conclusions: FMD is impaired in BD even in inactive state and IMT is greater despite a degree of statistical heterogeneity that reflects the clinical heterogeneity of BD. Future prospective studies should account for risk stratification of atherosclerosis in BD.

Introduction

Behcet's disease (BD) is a systemic vasculitis characterised by recurrent oral and genital aphthosis, ophthalmic, cutaneous, articular, intestinal, urogenital, neurological, pulmonary and vascular manifestations [1]. The prevalence of vascular involvement may be as high as 40% according to the ethnicity of the population under study [2] and superficial thrombophlebitis accompanies vascular occlusion in almost 13% of patients [3]. The vascular manifestations are prevalently venous thrombosis as well as aneurysm formation; occlusions in the superior and inferior vena cava, in the supra-hepatic vein and in the cerebral vein range between 3% and 41% [4]; aneurysms commonly develop in the pulmonary arteries but do not spare femoral, popliteal, subclavian and common carotid arteries [2]. Arterial disease ranges from 0.5% to 17% [2] and though the prevalence of myocardial is only 1.1%, it occurs in relatively young BD patients in their third decade of life [5] and may be silent in up to 25% of cases [6]. The standardized mortality ratio calculated from 428 BD patients was 10-fold higher than the reference population in the age group of 14–24 years, with pulmonary artery aneurysms and Budd–Chiari syndrome the leading cause of death followed by arterial disease, though the standardized mortality ratio decreased in older age groups [7]. Given the chronic inflammatory background of BD, the issue of premature atherosclerosis was addressed over the last decades with conflicting evidence [8]. We therefore assessed the available data by performing a systematic review and a meta-analysis of the studies where atherosclerosis was assessed by flow-mediated vasodilation (FMD) and endothelial-mediated vasodilation (EMD) and by measurement of the intima media thickness (IMT) of carotid arteries, noninvasive markers of endothelial health in

Abbreviations: FMD, flow-mediated dilatation; EMD, endothelial-mediated dilatation; IMT, intima media thickness; NOQAS, Newcastle Ottawa Quality Assessment Scale.

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humans [9,10]. Our designated outcomes were the difference in FMD/EMD measured at the brachial artery and IMT measured at the carotid arteries derived from studies comparing BD patients with groups of individuals deemed as healthy controls.

Methods

Search strategy and selection criteria

A systematic review according to the PRISMA guidelines was carried out [11]; the PubMed and EMBASE databases were searched with the following terms: BD, atherosclerosis, flow-mediated vasodilatation and endothelial dysfunction, intima media thickness and carotid. A preliminary search had not revealed any articles on the topic before January 2000 therefore, the final search spanned from January 2000 up to January 2014. Review articles, case reports and surveys on aneurysms regardless of the vascular districts were excluded. The reference list of retrieved papers was checked for references that could have been missed.

Criteria for selecting articles

Two investigators (M.M. and P.R.J.A.) independently assessed all the papers generated for relevancy and considered those observational case–control studies addressing the difference in mean brachial artery FMD and EMD and mean carotid artery IMT between BD patients and matched healthy controls. To be included in the review, the articles had to meet the following criteria: (1) BD patients and matched healthy controls had to be compared for FMD/EMD at the brachial artery and IMT at the common carotid artery and (2) the technique for brachial artery and carotid artery IMT measurement had to be based on similar published protocols [9,10]. Exclusion criteria were the following: (1) articles not written in English, (2) studies not comparing BD patients with healthy controls and (3) measurement of IMT of carotid arteries and of brachial artery FMD/EMD that deviated substantially from predefined protocols [9,10]. M.M. and P.R.J.A. screened all abstracts and applied the eligibility criteria in order to identify studies that were appropriate for inclusion. They independently extracted data using predefined criteria, which included date of publication, population, language, study design, 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; however, all the studies evaluated and included in the meta-analysis are simply comparing two different groups because they had no real exposure to qualify as true case–control [12]. The scoring system 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 the mean differences of FMD/EMD measured at the brachial artery and of IMT measured at the common carotid arteries. Data on mean values in both BD patients and matched healthy groups were collected to investigate the extent to which a pooled standardized mean difference between groups can be derived and considered as representative for BD patients. The secondary outcome was the difference of the pooled prevalence of subjects with carotid plaques derived from the BD and the healthy group.

Statistical analysis

Statistical analysis was carried out using STATA (StataCorp. 2013; Stata Statistical Software: Release 13; College Station, TX: StataCorp LP). Random effects meta-analyses for continuous outcomes (FMD, EMD and IMT) were employed as the estimates were the result of observational studies rather than planned experiments such as clinical trials. Besides clinical rich information, each study contained information on outcomes means, standard deviations and number of individuals in each group. The aim of the analysis was to investigate the average effect of the outcomes attributable to BD group; that is a standardized mean difference between BD patients and normal healthy individuals. Statistical heterogeneity among studies was assessed with chi square Cochran's Q test and with I^2 statistics, which measures the inconsistency across study results and describes the proportion of total variation in study estimates that are due to heterogeneity rather than sampling error. More specifically, an I^2 value of 0% indicates absence of heterogeneity and values less than 25% indicate low, between 25% and 50% moderate and over 50% high heterogeneity [13]. Subgroup analyses were based on clinical judgment, similarity of circumstances in which the studies have been conducted and the publication index. Whilst empirical methods such as Funnel plots [14,15] were part of preliminary investigations, the final estimates for an average effect on the BD outcomes relied on robust clinical and statistical compatibility, i.e., with evidence consistent with studies homogeneity [16]. Peto's method for pooled odds ratios was used to compare subjects with carotid artery plaques within BD and control groups because of its good performance when events are very rare [17].

Results

After completion of the screening process (Fig. 1), 24 studies met the criteria for inclusion in the analysis: 9 investigated FMD and/or EMD [18–26], 11 IMT [8,27–36] and 4 investigated both [37–40].

Quality of the studies

A score of ≥ 7 on the NOQAS was arbitrarily taken as a threshold for a good quality study: in the FMD/EMD section four studies ranked at ≥ 7 [19,21,23,26] (Table 1). In the IMT section part of the study only one study achieved a high score [8] (Table 2). Reasons for achieving a low score were poor selection criteria, poor documentation of patient and/or control inclusion/exclusion criteria, inadequate matching, poor comparability and failure to report disease duration and/or disease activity. The inter-rater reliability agreement of the two investigators (M.A. and P.R.J.A.) for NOQAS was 0.41 (95% CI: 0.0836–0.745) calculated by Cohen's kappa.

Analysis of flow-mediated vasodilatation

Data from 13 case–control studies comprising 554 patients with BD and 472 controls were pooled for the effect size of this outcome (Table 1). Random effect meta-analysis revealed wide heterogeneity amongst the studies ($I^2 = 95.6\%$, $p < 0.0001$) suggesting poor prospects for average pooled estimates. Having explored the causes for this heterogeneity, four studies [18,19,21,24] deviated slightly from the FMD methodology in that the cuff of the sphygmomanometer was applied at the forearm, a technique that yields a lower value than applying the cuff at the upper arm [41]. Removal of the four studies