Eur J Vasc Endovasc Surg (2016) 52, 333–342

REVIEW

Inflammation as a Predictor of Abdominal Aortic Aneurysm Growth and Rupture: A Systematic Review of Imaging Biomarkers

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Background: Methods are required to identify abdominal aortic aneurysms (AAAs) at increased risk of rupture. Inflammatory characteristics of AAA can be visualised using advanced imaging techniques and have been proposed as potential predictors of aneurysm progression. The objective of this review was to determine which inflammatory imaging biomarkers are associated with AAA growth and rupture.

Methods: A systematic review was carried out in accordance with the PRISMA guidelines. The electronic databases of Medline (PubMed), Embase, and the Cochrane Library were searched up to January 1, 2016 for studies to determine the potential association between inflammatory imaging biomarkers and AAA growth or rupture.

Results: Seven studies were included, comprising 202 AAA patients. ^{18}F-fluoro-deoxy-glucose positron emission tomography (^{18}F-FDG PET-CT) was evaluated in six studies. Magnetic resonance imaging with ultrasmall superparamagnetic particles of iron oxide (USPIO-MRI) was evaluated in one study. Two of six ^{18}F-FDG PET-CT studies reported a significant negative correlation ($r = .383$, $p = .015$) or a significant negative association ($p = .04$). Four of six ^{18}F-FDG PET-CT studies reported no significant association between ^{18}F-FDG uptake and AAA growth. The single study investigating USPIO-MRI demonstrated that AAA growth was three times higher in patients with focal USPIO uptake in the AAA wall compared to patients with diffuse or no USPIO uptake in the wall (0.66 vs. 0.24 vs. 0.22 cm/y, $p = .020$). In the single study relating ^{18}F-FDG uptake results to AAA rupture, the association was not significant.

Conclusions: Current evidence shows contradictory associations between ^{18}F-FDG uptake and AAA growth. Data on the association with rupture are insufficient. Based on the currently available evidence, neither ^{18}F-FDG PET-CT nor USPIO-MRI can be implemented as growth or rupture prediction tools in daily practice. The heterogeneous results reflect the complex and partially unclear relationship between inflammatory processes and AAA progression.

Article history: Received 1 February 2016, Accepted 2 May 2016, Available online 6 June 2016

Keywords: Aneurysm, Ruptured, Aortic aneurysm, Abdominal, Biomarkers, Diagnostic imaging, Growth, Inflammation

INTRODUCTION

Over recent decades imaging techniques have developed rapidly. Many of these have been explored in the search for methods that can identify abdominal aortic aneurysms (AAAs) with a high risk of rupture. One of the main areas of AAA imaging research is inflammation, as chronic inflammation with subsequent proteolytic degradation of the aortic wall is considered to be one of the principal causes of aortic wall weakening and aneurysm growth.[1]

Inflammatory processes can be evaluated indirectly using advanced imaging techniques that investigate the metabolic processes and energy consumption that represent inflammatory activity.[2,3] Examples of emerging techniques for these purposes include ^{18}F-fluoro-deoxy-glucose positron emission tomography (^{18}F-FDG PET-CT) and MRI using novel contrast agents such as ultrasmall superparamagnetic particles of iron oxide (USPIO). These techniques have been used to investigate atherosclerosis and unstable plaques.[4–8] ^{18}F-FDG and USPIO both accumulate in cells with high metabolic activity, such as macrophages, which are known for their high basal metabolic rate. Histological analyses of AAA specimens have validated that uptake of ^{18}F-FDG (a glucose analogue) and USPIO is linked to areas with macrophage activity and vessel wall inflammation.[9,10] By accumulating in macrophages, these biomarkers can serve

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http://dx.doi.org/10.1016/j.ejvs.2016.05.002

as markers for vessel wall inflammation, and potentially as markers for future AAA growth or rupture. Such biomarkers could assist in clinical decision making.

Many studies have been published on the application of these imaging biomarkers, and, in particular, ^{18}F-FDG PET-CT has received a lot of attention from researchers and clinicians. By writing this review we aim to determine how many of these techniques have been successfully translated into clinical studies with AAA, and might be ready to be used in clinical practice. The objective of this study is to determine which inflammatory imaging biomarkers are associated with AAA growth or rupture.

METHODS

We carried out a systematic review in accordance with the PRISMA guidelines,[11] strictly following a formal protocol which was written in accordance with the PRISMA-P statement.[12] The review protocol was registered in the PROSPERO database (registration number CRD42015024543).[13]

The online databases Medline (via PubMed), Embase (via OVID), and the Cochrane Library were searched for eligible articles. The date of the last search was January 1, 2016. The online International Clinical Trials Registry Platform (World Health Organization)[14] was searched for ongoing studies. No language or date restrictions were applied.

The literature search was performed with assistance from an experienced clinical librarian. The search strategy combined four sets of search terms, in accordance with the Patient-Intervention-Control-Outcome (PICO) methodology. The first set defined AAA, the second defined imaging techniques, the third defined inflammatory and metabolic processes, and the fourth defined aneurysm growth and rupture (Appendix S1, supplementary material).

Studies were eligible if they comprised an original study focusing on adult patients with an AAA, and investigated at least one diagnostic imaging technique focusing on the inflammatory, metabolic, cellular, or molecular properties of aneurysm tissue. Studies that did not relate the imaging results to aneurysm growth or rupture were not included. Also, studies were considered ineligible if they investigated patients with a mycotic AAA, patients who had undergone previous aortic repair, or patients who had concomitant diseases such as connective tissue disease or vasculitis. Reports of pilot studies describing fewer than five patients were excluded.

Two reviewers (HJ, RI) independently assessed all titles and abstracts for relevance. The full text of potentially relevant articles was retrieved and the same two reviewers assessed eligibility by consensus. Disagreements were solved by consulting a third reviewer (MK). If full text articles were not available, the corresponding authors were contacted. Reference lists from included articles were searched for other relevant articles.

Two reviewers (HJ, RI) independently extracted the data and afterwards merged the data by consensus. Data were processed in standardised data extraction forms. Corresponding authors were contacted for additional information if data were unclear or incomplete. Extracted data items included study design, objective, sample size, inclusion and exclusion criteria, patient characteristics, follow up period, funding source, technical aspects of imaging modalities, methods of measurement, interpretation of imaging results, and quantitative imaging results.

Study quality and risk of bias was assessed using a modified version of QUADAS-2[15] and Cochrane Collaboration's tool for assessing risk of bias.[16] The quality assessment included 10 individual measurements of selection, attrition, detection, and commercial bias. Studies were not excluded based on quality rating. The principal summary measure was the correlation of imaging biomarkers with clinical events as growth or rupture of the aneurysm.

RESULTS

The search strategy identified 1,933 unique articles (Fig. 1). After screening of titles and abstracts, 15 studies were marked as potentially relevant for inclusion by either investigator. Nine articles were selected for full-text review by consensus. After full-text review, two studies were excluded because they did not investigate a potential relationship between imaging results and AAA growth or rupture. One other study[17] was excluded because its patients overlapped with those of a more recent study by the same authors with a larger sample size.[18] One additional study was found through cross-referencing.[2] Subsequently, seven articles were included in this systematic review.

The characteristics of the included studies are presented in Table 1. Three studies were prospective,[10,18,19] three studies were prospective but used some retrospective data,[2,20,21] and one study did not clarify its design.[22] The total number of patients with an AAA in this review is 202. The sample size ranged from 14 to 47 patients (Table 1). Patient characteristics are summarised in Table 2. Six articles[2,18–22] investigated analyses with ^{18}F-FDG PET-CT and one study[10] investigated the application of USPIO-enhanced MRI. The technical details of the imaging techniques are presented in Appendix S2 (supplementary material). All included articles originated from European countries.

Five studies related the imaging results (^{18}F-FDG PET-CT and USPIO-MRI) to multiple AAA growth measurements over a longer period of time.[2,10,18,19,21] Three of these studies measured growth using ultrasound (US),[10,18,21] one study used computed tomography angiography (CTA),[19] and one study did not clarify the technique used for growth measurements.[2] Two studies related ^{18}F-FDG PET-CT imaging results obtained at a single point in time with the occurrence of clinical events during follow up.[20,22]

The overall findings of the risk of bias assessment were: a low risk of selection and commercial bias, a varied risk of attrition and detection bias, and a high risk of outcome reporting bias (Table 3). Software support was provided by software companies in two studies.[18,20] In one of the studies, one co-author was scientific director of the commercial software company.[18]