Abdominal aortic aneurysms

The quest for meaningful biomarkers and opportunities to improve surgical care

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CHAPTER 1

Inflammation as a predictor of abdominal aortic aneurysm growth and rupture: A systematic review of imaging biomarkers

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ABSTRACT

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 PETCT 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.

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 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 (Figure 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]

The main results of the individual studies are presented in Table 4.

^{18}F-FDG PET-CT

Six studies investigated ^{18}F-FDG uptake as a marker of metabolic activity and inflammation using PET-CT.[2,18-22] Two studies (Sakalihasan et al.,[22] Nchimi et al.[20]) found a non-significant positive association between ^{18}F-FDG uptake and growth, whereas two studies (Kotze et al.,[21] Morel et al.[19]) found a significant negative correlation, and two studies (Kotze et al.,[21] Reeps et al.[2]) found no significant correlation.

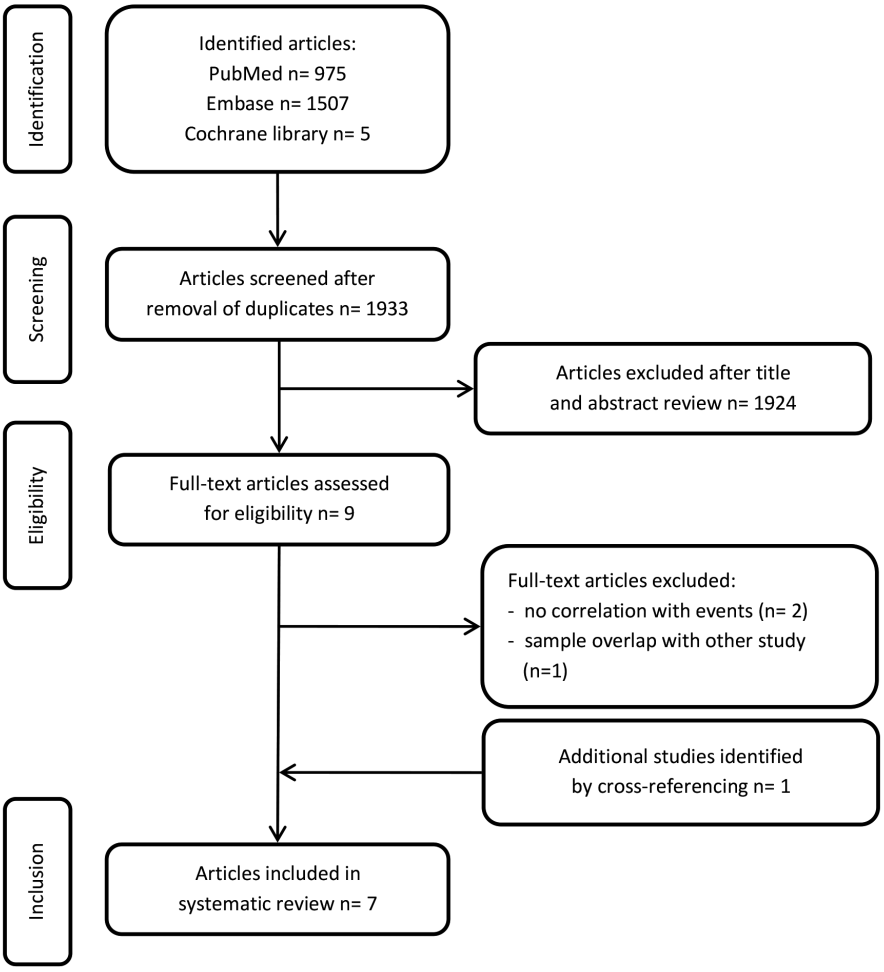

Figure 1. Study selection flowchart

Five of six studies quantified the ^{18}F-FDG uptake with the standardised uptake value (SUV_{max}).[2,18,21] SUV_{max} is the most commonly used unit for measuring ^{18}F-FDG accumulation and metabolic activity in tissues with PET imaging. A higher SUV_{max} represents higher metabolic (and inflammatory) activity. Numerical values of ^{18}F-FDG uptake results are presented in Appendix S3 (supplementary material). Two studies calculated tissue-to-background ratios (TBR) by dividing the mean or average SUV_{max} by the mean activity of blood in the vena cava.[18,19]

The first ^{18}F-FDG PET-CT study was published by Sakalihasan et al., in 2002.[22] They

related ^{18}F-FDG uptake to clinical events prior to, or shortly after, PET-CT imaging (<30 days), in 26 patients. A possible association was detected between increased ^{18}F-FDG uptake and previous rapid growth, defined as growth >5 mm in 6 months. Four of 10 patients in the PET-positive group had rapid growth vs. two out of 16 in the PET-negative group (p = .16, Fisher's exact test). Unfortunately, no definition was given for positive ^{18}F-FDG uptake.

Nchimi et al. (2014) performed a single ^{18}F-FDG PET-CT analysis in 47 patients with AAA.[20] ^{18}F-FDG uptake was considered positive if a radiologist identified ≥ 1 area with >1 cm of increased signalling in the aneurysm wall. After a follow up period of 30 months, they detected rapid growth (defined as >1 cm/y) in two of 13 PET-positive AAAs and in two of 34 PET-negative AAAs (p = .30, Fisher's exact test). There were no ruptures in either group.

Kotze et al. (2014) investigated the relationship between ^{18}F-FDG uptake and AAA growth, as measured by US at baseline and after 6 and 12 months follow-up in 40 patients.[18] This study found that AAAs with a higher annual growth rate at 12 months actually had a lower SUV_{max} at baseline (weak negative correlation; r =-.383, p = .015). ^{18}F-FDG uptake was determined by the concentration of ^{18}F-FDG (in kBq/g) in aortic tissue, adjusted for injected ^{18}F-FDG dose, ^{18}F-FDG decay, body weight, and for background metabolic activity. As an explanation for the negative correlation, the authors state that an earlier inflammatory phase possibly preceded the non-inflammatory dilatation phase.

Morel et al. (2015) performed both ^{18}F-FDG PET-CT and CTA, at baseline and at 9 months follow-up in 39 patients.[19] Similar to Kotze et al., they found that patients with significant growth (≥2.5 mm) had a lower SUV_{max} at baseline than patients without significant growth (mean 1.80, SD 0.45 vs. mean 2.21, SD 0.52; p = .04). The low ^{18}F-FDG uptake at baseline was no longer documented on the second ^{18}F-FDG PET-CT after nine months, suggesting a pattern of cyclic metabolic changes in the aneurysm wall.

Reeps et al.[2] (2008) carried out PET-CT imaging in 15 patients prior to elective or urgent open AAA repair. They compared the ^{18}F-FDG uptake results with histopathological characteristics of AAA wall biopsies. In addition, they compared the ^{18}F-FDG uptake results with retrospectively collected growth data, which were only available from seven patients. Growth was described as "annual" but the time interval and method of growth measurements were not reported. They found no significant correlation between SUV_{max} and previous annual growth (p = 0.15).

Likewise, Kotze et al.[21] (2009) measured the ^{18}F-FDG uptake in 14 patients with AAA under surveillance. Similar to Reeps et al., they compared the uptake results with retrospective growth data, as measured by two or more ultrasound scans. They found no significant correlation between SUV_{max} and previous annual growth (r =.18; p = .60).

Table 1. Characteristics of included studies

Author Year	Title	Study design	Sample size	Imaging technique	Imaging frequency	Imaging outcomes	Uptake definition	Diameter measurement technique	Diameter measurement frequency
Sakalihasan[22] 2002	Positron Emission Tomography (PET) Evaluation of Abdominal Aortic Aneurysm (AAA)	Cohort study	26	^{18}F-FDG PET-CT	1x	^{18}F-FDG uptake (positive / negative)	Not defined	Not defined	Not defined
Nchimi[20] 2014	Multifactorial relationship between ^{18}F-fluoro-deoxy-glucose positron emission tomography signalling and biomechanical properties in unruptured aortic aneurysms	Prospective cohort study with retrospective growth data	47	^{18}F-FDG PET-CT	1x	- SUV_{RL}, SUV_{RV} - TBR_{max}	Positive uptake: ≥ 1 area with >1 cm of increased signalling compared with the intra-arterial background and distant aortic wall segments	PET-CT	Unclear: Baseline and follow-up
Kotze[18] 2014	CT signal heterogeneity of abdominal aortic aneurysm as a possible predictive biomarker for expansion	Prospective multicentre cohort study	40	^{18}F-FDG PET-CT	1x	CTTA: - Stand Dev (SD) - Kurtosis (k) PET/CT: - SUV_{max} whole vessel - SUV_{max} single site - TBR_{max}	SUV value: The decay-corrected tissue concentration of ^{18}F-FDG (in kBq/g) adjusted for injected ^{18}F-FDG dose and body weight, and for background metabolic activity	Duplex ultrasound	3x - baseline - 6 months - 12 months
Morel[19] 2015	Evidence of Cyclic Changes in the Metabolism of Abdominal Aortic Aneurysms During Growth Phases: ^{18}F-FDG PET Sequential Observational Study	Prospective cohort study	39	^{18}F-FDG PET-CT	2x (baseline & 9 months)	- SUV_{max} whole vessel - TBR_{max}	SUV value: Calculated by dividing the activity measured in each voxel by the total injected activity expressed per gram of body weight and corrected for radioactive decay	CTA	2x: - baseline - 9 months

Author Year	Title	Study design	Sample size	Imaging technique	Imaging frequency	Imaging outcomes	Uptake definition	Diameter measurement technique	Diameter measurement frequency
Kotze[21] 2009	Increased metabolic activity in abdominal aortic aneurysm detected by 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography / computed tomography (PET/CT)	Prospective cohort study with retrospective growth data	14	^{18}F-FDG PET-CT	1x	SUV_{max}	Maximum Standardised Uptake Value (SUV_{max}) was measured in the aneurysm area with most intense wall 18F-FDG uptake.	Ultrasound	Varying intervals: 3, 6, or 12 months prior to PET-CT
Reeps[2] 2008	Increased 18F-fluorodeoxyglucose uptake in abdominal aortic aneurysms in positron emission / computed tomography is associated with inflammation, aortic wall instability, and acute symptoms	Prospective cohort study with retrospective growth data	15	^{18}F-FDG PET-CT	1x	SUV_{max}	Areas with maximum ^{18}F-FDG uptake were visually detected and the SUV_{max} was obtained by computational analysis	Not defined	Not defined
Richards[9] 2011	Abdominal aortic aneurysm growth predicted by uptake of ultrasmall superparamagnetic particles of iron oxide: a pilot study	Prospective cohort study	29	USPIO-MRI	1x	USPIO uptake in wall or thrombus (high, low, unspecific)	Positive uptake: Threshold of > 59% change of T2* value (constant decay value of signal intensity) after contrast administration	Ultrasound	2x - before MRI - after MRI (6 month interval)

Table 2. Patient characteristics across studies

Author	n=	Male sex	Mean age	AAA baseline diameter	Symptomatic AAA	Smoking history	Hyper-tension	Diabetes mellitus	Ischaemic heart disease
Sakalihasan[22]	26	88% (23/26)	72	mean 63 mm, range 45 - 78 mm	11 / 26	-	-	-	-
Nchimi[20]	47	85% (45/53)*	72*	mean 42.6, SD ± 10.3 mm	-	43/53*	32/53*	11/53*	37/53*
Kotze[18]	40	90% (36/40)	74	median 49.5 mm, IQR 43.0 - 53.0 mm	0 / 40	22/40	31/40	4/40	13/40
Morel[19]	39	95% (37/39)	71	median 51.0 mm, IQR 41.0 - 55.8 mm	0 / 39	37/39	22/39	5/39	15/39
Kotze[21]	14	100% (14/14)	74	mean 54 mm, SD ± 8 mm	1 / 14	6/14	6/14	1/14	2/14
Reeps[2]	15	87% (13/15)	69	mean 54 mm, SD ± 8 mm	3 / 15	12/15	14/15	6/15	8/15
Richards[9]	29	93% (27/29)	70	mean 52 mm, range 40 - 66 mm	0 / 29	29/29	17/29	4/29	12/29

* Includes 6 TAA patients

Three PET-CT studies included patients with symptomatic AAAs in their sample (Table 2). Sakalihasan et al.[22] (2002) included 11 symptomatic AAAs (from a total of 26 patients). Five of 10 patients in the PET-positive group were symptomatic, whereas six of 16 patients in the PET-negative group were symptomatic (p = .69, Fisher's exact test). Reeps et al.[2] (2008) included three symptomatic AAA patients (from a total of 14 patients). Mean ^{18}F-FDG uptake was significantly higher for the symptomatic patients compared with the asymptomatic AAA patients (mean SUV_{max}: 7.5, SD 0.3 vs. mean 3.5, SD 0.6, p < .001). Kotze et al.[21] (2009) included two inflammatory AAAs (from a total of 14 patients) of which one was symptomatic. A significant difference was found in the degree of ^{18}F-FDG uptake between the inflammatory AAAs and non-specific AAAs (p = .04).

CT texture analysis (CTTA)

The study of Kotze et al. (2014) included 40 patients and was the only study to investigate CT signal heterogeneity using CT texture analysis (CTTA).[18] CTTA has been applied in atherosclerosis and oncology research and is believed to detect areas of hypoxia and neovascularisation through texture analysis that assesses degrees of coarseness.[18] Kotze et al. used the commercially available TexRAD software (TexRAD Ltd, Somerset, UK) to filter CT images which were quantified using histogram-based parameters Kurtosis (K; reflecting the pointedness of the histogram) and standard deviation (SD; width of the histogram). It was demonstrated that medium texture Kurtosis was significantly, yet weakly, correlated with future AAA growth (r = .343, p = .030) during the 12-month follow-up. This correlation remained significant after adjustment for baseline size and

Table 3. Risk of bias within studies

	Consecutive enrollment? (selection bias)	Inappropriate exclusions avoided? (selection bias)	All patients completed study? (attrition bias)	Selective loss to follow-up excluded? (attrition bias)	Clear definition of index test (detection bias)	Clear definition of growth/event measurement (detection bias)	Blinding of index test (detection bias)	Blinding of growth/event measurement (detection bias)	Outcomes in prespecified protocol (outcome reporting bias)	Free of commercial funding (commercial bias)
Sakalihasan[22]	-	?	?	?	-	-	?	?	-	?
Nchimi[20]	?	+	?	?	+	-	?	?	-	+
Kotze[18]	+	+	-	-	+	+	+	+	-	+
Morel[19]	?	+	-	-	+	+	?	+	+	+
Kotze[21]	?	+	+	+	+	-	?	?	-	+
Reeps[2]	?	+	*	+	+	-	?	?	-	+
Richards[9]	?	+	-	+	+	+	+	?	+	+

* Patients completed the study, but retrospective growth data was incomplete.

after logistic regression adjusting for clinical variables such as sex, smoking, comorbidity, medication, etc. However, doubts could be raised about the validity of a logistic regression analysis in a sample of only 40 patients. Fine and coarse texture Kurtosis were not significantly associated with future growth. It has to be mentioned that at the moment, TexRAD software can only be used for research purposes. It has not received CE marking or FDA approval for usage as a medical device.

USPIO-MRI

One study (Richards et al.) investigated the uptake of USPIO with MRI in 29 patients with asymptomatic AAA.[10] To measure USPIO uptake, a MRI scan was performed before and at 24 - 36 h after intravenous USPIO administration. USPIO uptake was classified into three groups: no mural or thrombus USPIO uptake, diffuse USPIO uptake, and focal USPIO uptake. USPIO uptake was considered positive if the signal intensity decay value T2* was >59%. This previously identified threshold served to distinguish USPIO uptake from measurement variability. At baseline, there was no difference in aneurysm diameter between groups. AAA growth was determined from two ultrasound scans carried out 6 months apart, with one done before and the other after the MRI examination. Eleven patients with focal USPIO uptake had significantly higher growth rates compared with eight patients with diffuse and six patients with no USPIO uptake (focal uptake:

Table 4. Growth and rupture association results

Author	Growth	Rupture
Sakalihasan[22]	Rapid growth (>5 mm/6 mo): - PET-negative: 2 / 16 - PET-positive: 4 / 10	Acute rupture: - PET-negative: 0 / 16 - PET-positive: 1 / 10
Nchimi[20]	Rapid growth (>1 cm/y): - PET-negative: 2 / 34 - PET-positive: 2 / 13	Acute rupture/dissection: - PET-negative: 0 / 34 - PET-positive: 0 / 13
Kotze[18]	Correlation with 1 year expansion, adjusted for baseline AAA size: - ^{18}F-FDG; whole vessel SUV_{max}: *rs*= -0.383, p = 0.015 - CTTA; texture K: *rs* = 0.343, *p* = 0.030 - CTTA; coarse texture SD: *rs* = 0.312, *p* = 0.050	-
Morel[19]	Significant growth (≥2.5 mm/9 mo): SUV_{max}: 1.80 ± 0.45 Non-significant growth (<2.5 mm/9 mo): SUV_{max}: 2.21 ± 0.52 *p* = 0.04	-
Kotze[21]	Correlation between ^{18}F-FDG and recent AAA growth rate non-significant: *r* = 0.18; *p* = 0.60.	-
Reeps[2] *	Correlation between ^{18}F-FDG and recent AAA growth rate non-significant: *p* = 0.60.	-
Richards[9]	- Focal USPIO uptake: 0.66 cm/y - No USPIO uptake: 0.22 cm/y - Non-specific (diffuse) USPIO-uptake: 0.24 cm/y *p* = 0.020	-

* Growth data only available in 7 / 15 patients

0.66 cm/y, diffuse uptake 0.24 cm/y, no uptake 0.22 cm/y, p = .020). In addition, a positive moderate correlation was determined between the percentage of USPIO positive voxels with AAA growth (r = .46; p = .028).

USPIO was well tolerated by patients and no significant adverse events occurred. The research group of Richards et al. has recently started a prospective multicentre cohort study (MA3RS) to validate the USPIO technique within a larger population of 350 AAA patients during a 2-year follow-up (EudraCT: ISRCTN76413758).[23] Recruitment is complete and results are expected in 2017.

DISCUSSION

This systematic review shows contradictory results concerning the relationship between ^{18}F-FDG uptake and AAA growth in PET-CT studies. The results from the PET-CT studies vary widely and range from significant negative correlations to non-significant positive associations between ^{18}F-FDG uptake and AAA growth.[2,18-22] The single USPIO-MRI study reported a weak to moderate positive correlation between focal USPIO uptake

on MRI and AAA growth.[10] This method could be considered as possibly adequate for risk prediction, but the results of this single study need to be confirmed before clinical use in the future.

The contradictory ^{18}F-FDG uptake results reflect the deficit in understanding of the complex role of inflammation in AAA development. Chronic inflammation has long been believed to be an important factor in aneurysm formation. However, Morel et al. and Kotze et al. both actually demonstrated that low inflammatory activity preceded the growth phase.[18,19] This could be due to the reduced number of cells in fibrotic or necrotic regions of the aneurysm wall, but also due to cyclic changes in inflammatory activity. Hence, Morel et al. have demonstrated that the initial, reduced uptake is no longer present after the growth phase.

Doubts about the causative role of inflammation have also been fuelled by the fact that, to date, no medical anti-inflammatory intervention has been able to influence AAA progression.[24] The contradictory results of this review and the failure of anti-inflammatory drugs in AAA management seem to be part of the same wider issue of unidentified effects of inflammation in AAA pathophysiology.

The heterogeneous study samples could also have contributed to some of the contradictory ^{18}F-FDG PET-CT results. As Kotze et al. (2008) and Reeps et al. (2008) have demonstrated, ^{18}F-FDG uptake is significantly higher in symptomatic and inflammatory AAAs than in asymptomatic AAAs.[2,21] This could explain why the study of Sakalihasan et al. (which contained 11 painful AAAs [of 26 AAAs] and 4 inflammatory AAAs) demonstrated a positive association between ^{18}F-FDG uptake and growth.[22] Most other studies included primarily asymptomatic AAAs.

Differences in imaging techniques and differences between macrophage types could be another reason for the single USPIO-MRI study showing a positive association between USPIO uptake and growth, whereas two PET-CT studies showed a negative association or correlation between ^{18}F-FDG uptake and growth. An *in vitro* study with atherosclerotic plaques showed that pro-inflammatory M1 macrophages preferentially accumulated FDG, whereas M2 macrophages (which stimulate repair processes) accumulated both FDG and USPIO.[25] Others showed that ^{18}F-FDG and USPIO detect different stages of inflammatory processes.[26] In the aorta of atherosclerotic rabbits it was found that ^{18}F-FDG is more sensitive than USPIO in detecting early changes in plaque inflammation. These results further underscore the complexity of (visualising) inflammatory pro-cesses in the cardiovascular system.

Strengths and limitations

The aim of this review was to provide clinicians with an overview of imaging biomarkers for inflammation that could possibly predict AAA growth or rupture. We have purposely not included preclinical or *in vitro* investigations and have excluded studies containing

fewer than five AAA patients. The limited number of clinical studies and the heterogeneity among the studies rendered a meta-analysis impossible.

Because of the small number of studies included, a funnel plot analysis to quantify possible publication bias could not be performed. Our search of the International Clinical Trials Registry Platform[14] revealed no other unpublished investigations. However, publication bias in this review cannot be excluded, as this is a recognized problem in studies of test accuracy.[27]

The scoring system for quality assessment was specifically designed to detect significant reporting deficiencies in this review of prognostic imaging tests. We deliberately did not incorporate the individual quality items into one median quality score to avoid inaccurate conclusions on study quality. One noted strength was that three[10,18,19] of seven studies consisted of prospectively designed cohort studies and three others[2,20,21] were prospective but used growth data obtained retrospectively. However, only two studies had published the objectives in a pre-specified protocol.[10,19] As listed in Table 3, some items such as consecutive enrolment and items concerning blinding of observers were insufficiently reported in the studies, raising the possibility of selection and detection bias.

At study level, outcomes were limited by the small sample size of the studies, which ranged from 14 to 47 AAA patients. Furthermore, the follow-up time in the three prospective longitudinal studies[10,18,19] did not exceed 12 months. This follow up is obviously insufficient for smaller aneurysms, as growth over a short period of time is hard to detect accurately and rupture risk of small aneurysms is very low.

In addition, the methods of growth measurements varied considerably across studies and allow for substantial improvement in future studies. Only two studies mentioned blinding of the aortic diameter observers to other results.[18,19] Two studies[10,18] measured the maximum anteroposterior diameter, whereas Morel et al.[19] measured the diameter perpendicular to the long axis of the aneurysm. Four studies did not specify how the diameter was measured.[2,20-22] Furthermore, the intraobserver and interobserver variability could have influenced the accuracy of diameter measurements, as none of the studies mentioned whether the diameter measurements were performed by a single person, and only one study mentioned the interobserver variability (3.5%) for diameter measurements in their department.[10]

Future perspectives

As none of the available inflammatory imaging biomarkers are currently clearly associated with AAA growth or rupture, it is unlikely that any of them can be used for rupture prediction in the near future. Even if a solid association between these imaging biomarkers and AAA progression is found, the question remains as to how this can be translated to clinical decision making for an individual patient.

This question does not imply that future research with imaging techniques such as ^{18}F-FDG PET-CT or USPIO-MRI is futile. As tissue samples of smaller human AAAs are generally unavailable and histological evidence is lacking, in vivo imaging techniques must be used to understand the role of inflammation in AAA pathophysiology. For such investigations, further implementation of uniformity of both methodology and measurement units is necessary. To some extent, this is already the case in the ^{18}F-FDG PET-CT studies which use standardised values such as SUV_{max}. Such uniformity will not only aid in the future reproducibility of results, but will also ease pooling of quantitative results in future meta-analyses. Furthermore, larger cohorts are needed, as aneurysm growth does not occur in all patients with AAA and is especially hard to detect in smaller aneurysms. Considering that aneurysm development is a long process occurring over many years, a longer follow up period is also crucial.

In addition, to accurately detect growth patterns and find relationships with possible recurrent inflammation phases, high-frequency repetitive imaging is needed. Repetitive imaging using ^{18}F-FDG PET-CT will be limited by its associated harmful radiation dose. USPIO-MRI also has some safety concerns. The United States Food and Drug Administration (FDA) recently issued a boxed warning against the use of ferumoxytol as a therapeutic drug for the treatment of iron deficiency anaemia, after the occurrence of deadly anaphylactic reactions to the drug.[28] Despite the safety profile of ferumoxytol being similar to that of other common intravenous iron complexes,[29] and despite administration of USPIO as an imaging contrast medium appearing to be safe,[30,31] the FDA recommendations could limit its future use.

The techniques presented in this review are not the only methods available to visualise inflammatory characteristics of AAAs. Numerous research groups have experimented with techniques focusing on inflammatory characteristics of the vessel wall in preclinical studies. An elaborate narrative review focuses specifically on these emerging imaging techniques, which have mostly been investigated in animal models.[9] Many of these techniques target extracellular matrix remodelling, such as cathepsin imaging with activatable probes, labelled matrix metalloproteinase (MMP) inhibitors for PET or MRI, and nuclear imaging or MRI with tracers or contrast agents with affinity for MMPs.[9] Other techniques target angiogenesis through, for example, radio- or fluorescent dye-labelled vascular endothelial growth factor (VEGF) receptors, which have shown promising results for imaging angiogenesis in oncology and cardiovascular disease. However, the non-specific uptake of tracers and the variability in image acquisition and methodology have hindered the translation of these techniques into clinical studies.

Despite the current limitations, ^{18}F-FDG PET-CT and USPIO-MRI are interesting techniques for future investigations. Not as prediction tools, but to improve understanding of the role of inflammation in aneurysm development.

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APPENDIX S1
ELECTRONIC SEARCH

PubMed

("Aortic Aneurysm, Abdominal"[Mesh] OR abdominal aorta aneurysm* [tw] OR abdominal aortic aneurysm* [tw] OR aortic abdominal aneurysm* [tw])
AND
("Diagnostic Imaging"[Mesh] OR "Diagnostic Techniques, Cardiovascular"[Mesh]OR "Diagnostic Techniques, Radioisotope"[Mesh] OR scan*[tw] OR ultrasound*[tw] OR ultra-sound*[tw] OR angiograph*[tw] OR ultrasono*[tw] OR computed tomography[tw] OR CT[tw] OR CTA[tw] OR magnetic resonance imaging[tw] OR MRI [tw] OR MRA [tw] OR aortograph*[tw] OR imag*[tw] OR radiolog*[tw] OR doppler[tw] OR duplex*[tw] OR PET[tw] OR PET/CT[tw] OR PET-CT[tw] OR SPECT [tw] OR IVUS[tw] OR contrast-enhanced[tw] OR contrast-enhancement [tw] OR perfusion [tw] OR spectroscopy [tw])
AND
("Inflammation"[Mesh] OR "Immune System Processes"[Mesh] OR "Metabolism"[Mesh] OR "Proteins"[Mesh] OR "Cell Physiological Processes"[Mesh] OR "Genetic Processes"[Mesh] OR inflammat* [tw] OR metabolis*[tw] OR angiogene* [tw] OR neovascular*[tw] OR proliferat*[tw] OR function*[tw] OR antibod*[tw] OR enzym*[tw] OR phagocyt*[tw] OR remodeling[tw] OR activat*[tw] OR activit*[tw] OR apopto*[tw] OR molecular [tw] OR nano [tw] OR nanoparticle [tw] OR lyposom* [tw] OR macrophage* [tw])
AND
("Disease Progression"[MeSH] OR "Rupture, Spontaneous"[Mesh] OR "Aortic Rupture"[Mesh] OR progress*[tw] OR grow*[tw] OR expan*[tw] OR rupture*[tw] OR develop*[tw] OR dissecti*[tw] OR risk*[tw])
NOT
("Animals"[Mesh] NOT "Humans"[Mesh])
NOT
("Letter" [Publication Type] OR "Comment" [Publication Type] OR "Editorial" [Publication Type] OR "Review" [Publication Type])

EMBASE via Ovid

1. exp abdominal aorta aneurysm/ or (abdominal aortic aneurysm* or abdominal aorta aneurysm* or aortic abdominal aneurysm*).ab,kw,ti.
2. exp radiodiagnosis/ or exp "imaging and display"/ or exp echography/ or exp radioisotope/ or (imaging or image* or scan* or ultrasound or ultra-sound or ultrasono* or doppler or duplex* or IVUS or angiograph* or computed tomography or CT or CTA or magnetic resonance imaging or MRI or MRA or aortograph* or radiolog* or PET or PET/CT or PET-CT or SPECT or contrast enhanced or contrast enhancement or perfusion or spectroscopy).ab,kw,ti.
3. exp inflammation/ or exp immunity/ or exp *metabolism/ or exp protein/ or exp cell function/ or exp heredity/ or (inflammat* or metabolis* or angiogene* or neovascular* or proliferat* or function* or antibody* or enzyme* or phagocyt* or remodeling or activat* or activit* or apopto* or molecular or nano or nanoparticle or lymposom* or macrophage*). ab,kw,ti.
4. exp disease course/ or exp aorta rupture/ or (progress* or grow* or expan* or rupture* or develop* or dissect* or risk*). ab,kw,ti.
5. 1 and 2 and 3 and 4
6. exp animals/ or exp invertebrate/ or exp animal experiment/ or exp animal model/ or exp animal tissue/ or exp animal cell/ or exp nonhuman/
7. 6 not (human/ or normal human/ or human cell/)
8. 5 not 7
9. 8 not (conference review or editorial or letter or note or review).pt.

Cochrane Library

#1 = abdominal aortic aneurysm
#2 = imaging OR image OR radiology
#3 = cellular
#4 = molecular
#5 = metabolic
#6 = inflammation
#7 = #1 and #2 and (#3 or #4 or #5 or #6)

APPENDIX S2

Technical aspects of imaging modalities

Author	Imaging Technique	Imaging Frequency	Aspects CT(A) / MRI	Aspects FDG / USPIO	Work station / software	Image Analysis
Sakalihasan[22]	PET (FDG)	1x	Not reported	FDG: - Injection 3,7 mBq 18F-FDG/kg - Image 60 min. after injection - Prior fasting: 6h	- PET: SUNSparc, SUN Micro-system, Palo Alto, CA, USA	FDG uptake reviewed visually and defined as positive or negative.
Nchimi[20]	PET (FDG) CT	1x or more	PET-CT: - 5 mm collimation, 50 x 50 cm field-of-view (FOV), 120 kVp, pitch of 1.5:1, gantry rotation cycle of 0.8 s - PET-CT scanner Discovery LS (General Electrics Healthcare, Milwaukee, WI)	FDG: - Injection 3.7 MBq 18F-FDG/kg body weight - Image 54-100 min after injection - Prior fasting: 6h	- PET-CT: Advantage Windows release 4.3; GE Healthcare	FDG-PET: - Increased FDG uptake identified when increased signalling in at least 1 area >1 cm. Compared with intra-arterial background and distal aortic wall segments. - Volume of Interest (VOI) automatically selected. Mean and SD of FDG uptake in VOI estimated quantitatively using SUV. - Uptake description: diffuse, monofocal, plurifocal. - Maximal SUVs normalized as SUV-to-liver (SUV_{RL}) and SUV to-venous-background (SUV_{RV})
Kotze[18]	PET (FDG) CT + CTTA	1x	Combined PET-CT: - 64x3.75 mm detector, pitch 1,5, collimation 5mm (140 kVp and 80mA in 0.8 sec). - GE Healthcare Technology, Waukesha, WI, USA	FDG: - Injection 200 MBq 18F-FDG - Image 3 h after injection - Prior fasting: 6h	- TexRAD Ltd, Somerset UK - Xeleris workstation, GE Healthcare Technology, Waukesha, WI, USA	FDG-PET: - Whole vessel analysis with Region of interest (ROI) of the aneurysm wall. - SUV_{max} calculated for each axial level and whole abdominal aorta. - Tissue-to-Background Ratio calculated by dividing SUV_{max} by average blood ROI in vena cava. CTTA: initial band-pass image filtration technique using a Laplacian of Gaussian (LoG) filter to produce a series of derived images of the AAA displaying features at different anatomical scales from fine to coarse texture. AAA heterogeneity was quantified using histogram-based parameters including standard deviation (SD) and kurtosis.

Author	Imaging Technique	Imaging Frequency	Aspects CT(A) / MRI	Aspects FDG / USPIO	Work station / software	Image Analysis
Morel[19]	PET (FDG) CT	2x baseline and 9 months	Hybrid PET-CT: - 6-detector CT, 130 kV, 2-mm slice thickness, pitch of 1, 512 x 512 matrix. - Siemens: Biopgraph 6 True Point. CTA: - 64-detector, 100-140 kV, pitch ~1, 0.625 mm slice thickness, intensity adapted to noise index; rotation time of 0.6 s, 512 x 512 matrix. - LightSpeed VCT; GE Healthcare	FDG: - Injection 5.5 MBq/kg - Image 90 min after injection - Prior fasting: overnight	- PET-CT: Esoft station, Siemens - CTA: Volume Viewer; GE Healthcare	FDG-PET: - Reconstruction of FDG-PET images: Ordered-subset expectation maximization method (3 iterations and 8 subsets) with corrections for scatter and attenuation, displayed in 128 x 128 matrix with 3.0 x 3.0 x 3.0 voxels. - Whole vessel analysis with Region of interest and calculation of SUV_{max}. - Tissue to Background Ratio calculated by dividing SUV_{max} by mean blood voxel activity, estimated from the inferior vena cava.
Kotze[21]	PET (FDG) CT	1x	PET-CT: - 64 detector, 140 kVp, 80mA in 0.8 s, 1.5 pitch, 5 mm collimation, 3,27 mm slice thickness - GE Healthcare Technology, Waukesha, WI	FDG: - Injection 175 MBq - Image 3 h after injection - Prior fasting: 6 h	Xeleris workstation, GE Healthcare Technology, Waukesha, WI, USA	FDG-PET: - Volume of interest placed on the aneurysm area with most intense aortic wall ^{18}F-FDG uptake - Measurement of the maximum Standardised Uptake Value (SUV_{max}).
Reeps[2]	PET (FDG) CT	1x	PET-CT: - 16 detector, 120 kV, 20 mAs, 3 mm slice thickness - Siemens Biograph Sensation 16, Erlangen, Germany	FDG: - Injection 370 MBq - Image 90 min after injection - Prior fasting: 6 h	- CT: Volume Wizard workstation (Siemens Medical Solutions, Erlangen, Germany) - PET: Syngo workstation and True D software (Siemens Medical Solutions)	FDG-PET/CT scans were visually analysed on the workstation. The superimposed CT and PET images were assessed for aneurysm morphology and distribution of FDG tracer uptake. Areas with maximum focal FDG uptake were visually detected, and SUV_{max} in each aneurysm was obtained by computational analyses.

Author	Imaging Technique	Imaging Frequency	Aspects CT(A) / MRI	Aspects FDG / USPIO	Work station / software	Image Analysis
Richards[9]	MRI (USPIO)	1x	MRI - Whole-body 3-T Verio scanner - Performed 24 h before and 36 h after administration of USPIO - Additional ECG-triggered T2-weighted turbo spin sequence - Siemens Magnetom Verio (Erlangen, Germany)	USPIO: - Weight-adjusted dose of 2.6 mg/kg (diluted in 100 mL 0.9% saline) administered as infusion in 30 minutes - Manufacturer: Sinerem, Guerbet (France)	x	- Semiautomatic rigid 3D voxel registration protocol (Analyze, Mayo clinic). - Region of interest encompassed aortic wall and thrombus drawn on each slice of precontrast T2W image. - The percent change in T*value after USPIO administration was calculated on a voxel-by-voxel basis and displayed on a colour scale (significance threshold: 59%).

APPENDIX S3

^{18}F-FDG uptake results

Author	SUV_{max} single site Baseline	SUV_{max} whole vessel Baseline	SUV_{max} whole vessel Follow-up	TBR whole vessel Baseline	TBR whole vessel Follow-up
Nchimi[20]	SUV_{RL}: - Mean: 0.68 - SD: 0.15 SUV_{RV}: - Mean: 1.22 - SD: 0.28	-	-	-	-
Kotze[18]	- Median 1.796 - IQR 1.500-2.402	- Median 1.798 - IQR 1.463-2.256	-	- Median: 1.200 - IQR 1.100 - 1.506	-
Morel[19]	-	- Mean: 2.12 - SD: 0.53	9 months: - Mean: 2.17 - SD: 0.69	- Mean 1.55 - SD: 0.28	9 months: - Mean 1.65 - SD: 0.43
Kotze[21]	- SUV_{max} >2.5 (increased) in 12/14 AAA - SUV_{max} ≤ 2.5 (normal) in 2/14 AAA - range: 2.2 – 6.5	-	-	-	-
Reeps[2]	SUV_{max} of asymptomatic AAA: - mean 3.5 - SD: 0.6 SUV_{max} of symptomatic AAA: - mean 7.5 - SD 0.3				

SUV_{RL}: SUV-to-liver ratio, SUV_{RV}: SUV-to-venous background ratio.