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A systematic review summarizing local vascular characteristics of aneurysm wall to predict for progression and rupture risk of abdominal aortic aneurysms

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ABSTRACT

Objective: At present, the rupture risk prediction of abdominal aortic aneurysms (AAAs) and, hence, the clinical decision making regarding the need for surgery, is determined by the AAA diameter and growth rate. However, these measures provide limited predictive information. In the present study, we have summarized the measures of local vascular characteristics of the aneurysm wall that, independently of AAA size, could predict for AAA progression and rupture.

Methods: We systematically searched PubMed and Web of Science up to September 13, 2021 to identify relevant studies investigating the relationship between local vascular characteristics of the aneurysm wall and AAA growth or rupture in humans. A quality assessment was performed using the ROBINS-I (risk of bias in nonrandomized studies of interventions) tool. All included studies were divided by four types of measures of arterial wall characteristics: metabolism, calcification, intraluminal thrombus, and compliance.

Results: A total of 20 studies were included. Metabolism of the aneurysm wall, especially when measured by ultra-small superparamagnetic iron oxide uptake, and calcification were significantly related to AAA growth. A higher intraluminal thrombus volume and thickness had correlated positively with the AAA growth in one study but in another study had correlated negatively. AAA compliance demonstrated no correlation with AAA growth and rupture. The aneurysmal wall characteristics showed no association with AAA rupture. However, the metabolism, measured via ultra-small superparamagnetic iron oxide uptake, but none of the other measures, showed a trend toward a relationship with AAA rupture, although the difference was not statistically significant.

Conclusions: The current measures of aortic wall characteristics have the potential to predict for AAA growth, especially the measures of metabolism and calcification. Evidence regarding AAA rupture is scarce, and, although more work is needed, aortic wall metabolism could potentially be related to AAA rupture. This highlights the role of aortic wall characteristics in the progression of AAA but also has the potential to improve the prediction of AAA growth and rupture. (J Vasc Surg 2023;77:288-98.)

Keywords: Abdominal aortic aneurysm; Aortic wall; Growth; Rupture

Abdominal aortic aneurysms (AAAs) have a multifactorial pathogenesis, characterized by elastin and collagen degradation in the aortic wall, apoptosis of vascular smooth muscle cells, and infiltration of leukocytes into the aneurysmal tissue.[1,2] Furthermore, vascular inflammation is the key process underlying AAA development and progression.[3-6] AAA rupture is a devastating complication that occurs when the local wall stress exceeds the wall strength, resulting in intra-abdominal hemorrhage with mortality of 85%.[7] In general, AAA patients are asymptomatic and, therefore, AAAs are mostly diagnosed as an incidental observation on imaging studies performed for other pathology or when they present with rupture.[8] This highlights the importance of accurate predictions for the risk of AAA rupture.

The current predictions for the risk of AAA rupture and, consequently, the indications for preventive treatment, are determined by the maximum anteroposterior diameter and the growth rate. The maximum anteroposterior

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diameter is measured perpendicular to the center line using three-dimensional reconstructed computed tomography (CT) images. Studies have shown that the risk of AAA rupture is strongly associated with the AAA diameter.[9-11] However, a recent study by Oliver-Williams et al[12] had included 18,652 men with small (3-4.4 cm) and medium (4.5-5.4 cm) AAAs. Of the 18,652 men, 31 had experienced a ruptured AAA during surveillance, resulting in a risk of 0.03% per annum for men with small AAAs and 0.28% for those with medium AAAs.[12] In a cohort of 192 ruptured AAAs, 7.2% had had a diameter <5.5 cm.[13] The rupture rates of untreated large AAAs were lower (range, 3.5%-6.3%) than those currently reported in the literature.[14] Laine et al[15] also demonstrated that 6% of men and 12% of women had had a ruptured AAA that had been below the threshold for repair.[15] These findings emphasize the need for additional, personalized measures that can predict the risk of AAA rupture, independently of AAA size, to optimize personalized patient care.

The pathogenesis of AAAs involves several crucial mechanisms occurring in the aortic wall, including inflammation,[4,5] biomechanical changes,[3] and calcification.[4,6] Accordingly, these processes affect the functional aortic wall characteristics that, subsequently, contribute to the increased risk of AAA growth and rupture. It is possible that directly measuring these aortic wall characteristics, including functional changes and inflammation, might better aid in the prediction of AAA progression and the risk of rupture compared with the AAA size. Therefore, the aim of the present systematic review is to summarize the potential measures of aneurysmal wall characteristics that, independently of AAA size, can predict for AAA progression and AAA rupture in patients with AAA who are not yet suitable for treatment.

METHODS

The present review was conducted and reported in accordance with the 2009 PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement. An identifier (CRD42020177659) for our protocol was assigned at PROSPERO (available at: https://www.crd.york.ac.uk/prospero/). The PubMed and Web of Science databases were searched on May 11, 2020, and the search was updated on September 13, 2021. Only primary sources were included in the review. The references of the included studies and secondary sources were manually searched for additional relevant studies that had been missed by the electronic search. The search strategy for each database is shown in Supplementary Table I (online only). The search strategy included the different elements of the PICO (population, intervention, comparison, and outcome) tool. The target population consisted of adult patients with an AAA who had not yet been treated. The "Intervention" were the measures of the local vascular wall characteristics in the aneurysm wall. These distinct measures were compared among each other. The outcome was defined as AAA growth and/or rupture.

Eligible studies were required to have investigated at least one measure of aneurysmal wall characteristics combined with its prognostic value for AAA rupture risk and/or AAA growth, preferably independently of the current clinically used risk factor (eg, baseline aorta diameter). The local aneurysmal wall characteristics were defined as the vascular functional properties of the aortic wall. The exclusion criteria were language other than English, animal studies, and in vitro studies.

The studies identified through the electronic search were independently screened by title and abstract by two of us (J.J.M.V., M.M.) using Rayyan (Rayyan Systems Inc, Cambridge, MA).[16] Subsequently, the potentially relevant studies were independently assessed for eligibility by two of us (M.M., F.B.G.d.V.). Disagreements were resolved in a consensus meeting (J.J.M.V., M.M., F.B.G.d.V.). For the quality assessment, the ROBINS-I (risk of bias in nonrandomized studies of interventions) tool was used to evaluate all included studies by two of us (M.M., F.B.G.d.V.) independently.[17] Differences in the quality assessment results were resolved in a consensus meeting (J.J.M.V., M.M., F.B.G.d.V.).

All included studies were divided into four groups according to the vascular wall characteristic studied: metabolism, calcification, intraluminal thrombus (ILT), and compliance. When the studies had investigated more than one wall characteristic, the study was classified according to the study's primary focus. The metabolism was measured using three different measures: (1) ^{18}F-fluorodeoxyglucose (FDG) uptake (the most commonly used contrast agent to visualize the aortic metabolism) in the aneurysm wall, which was evaluated using positron emission tomography combined with either CT[18] or magnetic resonance imaging (MRI)[19]; (2) ^{18}F-sodium fluoride (NaF) uptake evaluated by positron emission tomography/CT[20]; and (3) ultra-small superparamagnetic iron oxide (USPIO) uptake evaluated by MRI.[21,22] All measures had used contrast agents to visualize aneurysmal wall inflammation. Calcification was measured using different scores to define the amount of calcification in the aneurysm wall from ultrasound or CT images in the identified studies.[23-27] Various parameters related to ILT were reported, including ILT thickness, deposition, area, volume and, volume change, to define ILT in relation to growth or rupture. CT had been used in four studies[28-31] and MRI in one study[32] to visualize ILT. All the studies had used ultrasound (echo-tracking[33]) as an imaging modality to measure aneurysmal wall compliance, described as stiffness and elastic modulus was calculated using the same formulas for all the studies.[34-38]

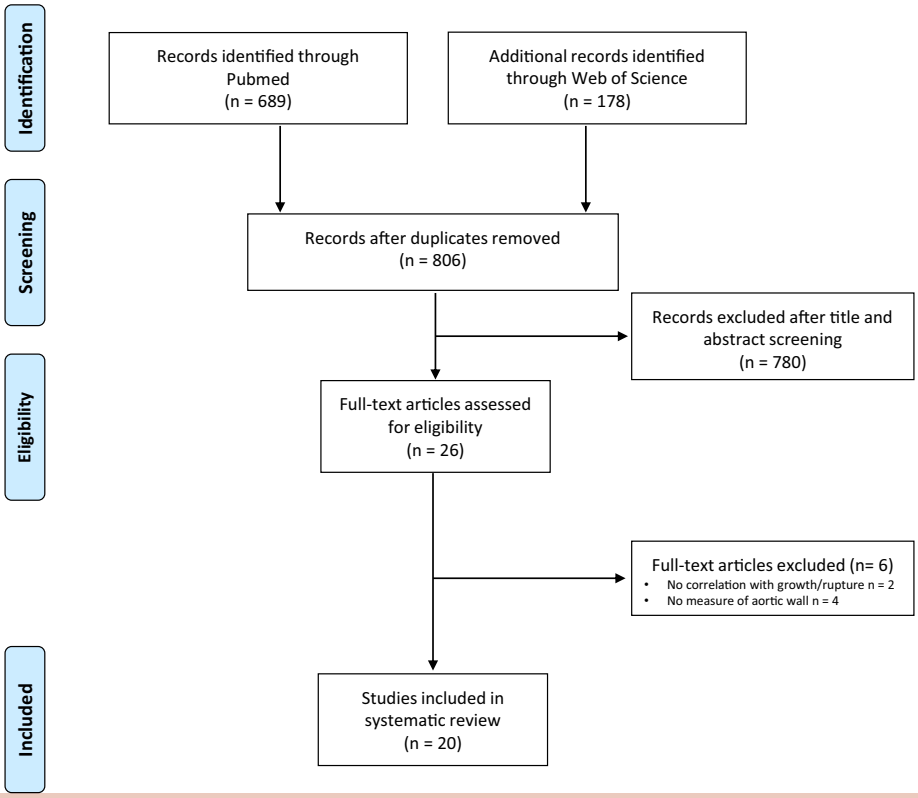

Fig. Flowchart describing inclusion of eligible studies.

RESULTS

The search strategy identified 806 unique studies, which were screened by title and abstract (Fig). Of the 806 studies, 780 were excluded, leaving 26 potentially relevant reports for the full-text review. Of the 26 studies, 2 were excluded because they had not correlated the aneurysmal wall changes with AAA growth and/or rupture and 4 because they had not used a measure linked to the aneurysm wall. Thus, 20 studies had met the inclusion criteria and were included in the present systematic review.

Prediction of AAA growth

Metabolism. Originally, studies had used ^{18}F-FDG to measure local artery metabolism. However, these had reported conflicting results regarding ^{18}F-FDG uptake in relation to AAA growth (Table I). One prospective study with a small sample size (n = 34) had demonstrated an inverse correlation between metabolism, as measured by ^{18}F-FDG uptake, and AAA growth.[18] Another retrospective study with 15 participants found a moderate correlation between the number of FDG hotspots and recent AAA growth.[19] More recent studies had used ^{18}F-NaF and USPIO uptake to measure local artery metabolism. One study of a prospective cohort (n = 72) had used ^{18}F-NaF uptake and found a positive correlation between ^{18}F-NaF uptake in the aneurysm wall and the AAA growth rate.[20] Studies investigating USPIO uptake demonstrated a higher growth rate in AAAs with USPIO uptake than in those without USPIO uptake.[21,22] One of these studies was a prospective study of 342 patients and a median follow-up time of 33.5 months.[22]

Calcification. Three studies had correlated the aneurysmal wall calcification volume with AAA growth (Table II).[23-25] One retrospective study by Hendy et al[24] (n = 88) had found no significant relationship between the aneurysmal wall calcification volume and AAA growth rate. In contrast, two larger studies, one prospective (n = 122) and one retrospective (n = 414), had demonstrated an inverse effect between the aneurysmal wall calcification volume and AAA growth rate, with larger calcification volumes associated with an attenuated growth rate.[23,25]

Intraluminal thrombus. Studies investigating ILT in relation to AAA growth had used multiple parameters to define the presence of ILT in the AAA (Table III). Three small retrospective studies, with sample sizes of 26 to 34 participants, showed conflicting results regarding the ILT volume in relation to AAA growth. Although one study had found a positive correlation between a larger ILT volume and larger growth rate,[28] the others had found a negative correlation[30] or no difference[29] in ILT volume between high and low growth rate AAAs. Another study had investigated a

Table I. Details of included studies of metabolism of aortic wall as measuring type

Investigator	Study design (FU; months)	Sample size, No.	Measuring type (technique)	Outcome		Main findings for association with growth/rupture
				Growth	Rupture	
Kotze et al,[18] 2011	Prospective cohort (12)	34	^{18}F-FDG SUV_{max} (^{18}F-FDG PET/CT)	Aneurysm diameter	–	Inverse correlation between whole vessel ^{18}F-FDG SUV_{max} and ultrasound expansion at 1 year ($r = -0.50$; $P = .01$)
Richards et al,[21] 2011	Prospective cohort (6)	29	USPIO uptake in aortic wall (USPIO-enhanced MRI)	Aneurysm diameter	–	Patients with distinct focal areas of increased USPIO uptake had threefold higher aneurysm growth rates vs patients with no or nonspecific USPIO uptake ($P = .02$)
Kuzniar et al,[19] 2019	Retrospective cohort (ND)	15	Aneurysm wall LGE and TBR_{max}, FDG hotspots (SUV_{max}) (^{18}F-FDG PET/MRI)	Aneurysm diameter	–	Significantly higher growth rates in LGE-positive vs LGE-negative aneurysms (7 mm/y vs 2 mm/y; $P = .03$); recent AAA growth correlated positively with number of FDG hotspots ($r = 0.62$; $P = .013$) but not with FDG hotspot SUV_{max} ($r = 0.198$; $P = .48$) or TBR_{max} in aneurysmal wall ($r = 0.406$; $P = .13$)
Forsythe et al,[20] 2018	Prospective cohort (17)	72	^{18}F-NaF SUV_{max} (^{18}F-NaF PET/CT)	Aneurysm diameter	Confirmed by autopsy	Higher expansion rate in tertile 3 of ^{18}F-NaF uptake in AAA patients (3.10 mm/y) vs tertile 1 (1.24 mm/y) and tertile 2 (1.55 mm/y; $P = .008$); no significant difference in rupture events between tertile 1 (1/24), tertile 2 (2/24), and tertile 3 (0/24)
Forsythe et al,[22] 2018	Prospective cohort (33.5)	342	USPIO enhancement in aneurysm wall (USPIO-enhanced MRI)	Aneurysm diameter	Confirmed by clinical end point committee	USPIO-enhanced vs non –USPIO-enhanced aneurysm showed higher aneurysm growth rates (3.1 ± 2.5 mm/y vs 2.5 ± 2.4 mm/y; $P = .04$) and more rupture events (10/146 vs 7/191; $P = .19$)

AAA, Abdominal aortic aneurysm; *CT*, computed tomography; *FDG*, fluorodeoxyglucose; *FU*, follow-up; *LGE*, late gadolinium enhancement; *MRI*, magnetic resonance imaging; *NaF*, sodium fluoride; *ND*, not determined; *PET*, positron emission tomography; SUV_{max}, maximum standardized uptake value; TBR_{max}, maximum target/background ratio; *USPIO*, ultra-small superparamagnetic iron oxide.

wide variety of parameters to define ILT in a prospective cohort of 41 participant and found AAA growth correlated with the baseline ILT volume but not the ILT volume growth.[32]

Compliance. Three studies had investigated aneurysmal wall compliance, defined as the elastic modulus, stiffness, or incremental Young's modulus, in relationship to AAA growth (Table IV). One small (n = 7) prospective study with a follow-up time of 48 months found a higher relative increased elastic modulus in fast growing (ie, 6-12 mm) AAAs (elastic modulus range, 75%-700%) compared with medium (ie, 5-6 mm) AAAs (elastic modulus range, 25%-125%) or no growth (ie, <2 mm) AAAs (elastic modulus range, −10% to 100%).[35] However, two larger studies with 60 and 326 participants found no relationship between the elastic modulus or stiffness of the aneurysm wall and AAA growth.[34,36]

Prediction of AAA rupture

Metabolism. Two prospective studies had investigated the relation between AAA metabolism and rupture events (Table I). One study, with the smallest sample size (n = 72), had recorded three events of rupture and found no difference in the rupture events between AAAs with different ^{18}F-NaF uptake.[20] Another larger multicenter study (n = 342) had mainly focused on the composite end point of AAA rupture and repair.[22] When investigating the 17 rupture events, the AAAs with USPIO

Table II. Details of included studies of calcification as measuring type

Investigator	Study design (FU; months)	Sample size, No.	Measuring type (technique)	Outcome		Main findings for association with growth/rupture
				Growth	Rupture	
Lindholt,[23] 2008	Prospective cohort (73.8)	122	Degree of calcification (B-mode ultrasound)	Aneurysm diameter	–	Patients with AAA wall calcification (ie, >50%) showed less growth (1.72 mm/y vs 2.97 mm/y; P = .001)
Hendy et al,[24] 2015	Retrospective cohort (16)	88	Infrarenal aortic calcification volume (CT)	Aneurysm diameter and volume	–	Above vs below median calcification: no differences in diameter (1.8 mm/y vs 1.6 mm/y; P = .99) or volume (7.8 cm^3/y vs 6.0 cm^3/y; P = .66)
Nakayama et al,[25] 2016	Retrospective cohort (19.2)	414	Percentage of calcification (CT)	Aneurysm diameter	–	Calcification inversely related to AAA expansion
Siegel et al,[26] 1994	Retrospective case control (ND)	108	Thrombus size; calcification (CT)	–	Confirmed by clinical course, surgery, or autopsy	Focal discontinuity in circumferential calcification seen in 8% of ruptured AAAs; significantly less thrombus (2.04 vs 2.29; P = .01) and thrombus calcification (13% vs 25%; P =.01) in ruptured AAAs vs nonruptured AAAs
Buijs et al,[27] 2013	Retrospective case control (ND)	334	AAC-8 score (CTA)	–	Confirmed by CTA or surgery	Significantly higher AAC-8 scores with symptomatic (P < .05) and ruptured (P < .05) AAAs vs elective AAA

AAA, Abdominal aortic aneurysm; *AAC-8*, abdominal aortic calcification-8; *CT*, computed tomography; *CTA*, computed tomography angiography; *FU*, follow-up; *ND*, not determined.

uptake had had more rupture events (6.8%) than those without USPIO uptake (3.7%), albeit the difference was not statistically significant.[22]

Calcification. Calcification was scored differently in the two studies that had investigated the relationship of calcification to AAA rupture (Table II).[26,27] Buijs et al[27] performed a retrospective study of a cohort of 334 patients, of whom 73 patients had had a ruptured AAA. The ruptured AAAs had had significantly higher calcium scores compared with age- and gender-matched intact AAAs. Another retrospective case-control study of 108 AAA patients found no differences in the calcification classification between the ruptured (n = 52) and non-ruptured (n = 56) AAAs.[26]

Table III. Details of included studies of intraluminal thrombus as measuring type

Investigator	Study design (FU; months)	Sample size, No.	Measuring type (technique)	Outcome		Main findings for association with growth/rupture
				Growth	Rupture	
Speelman et al,[28] 2009	Retrospective cohort (9)	30	ILT volume (CTA)	Aneurysm diameter	–	Above vs below median ILT volume: significantly higher growth rate for AAAs with ILT volume above median (above: 3 mm; IQR, 1-6 mm; below: 0 mm; IQR, 0-1.2 mm; $P < .01$).
Metaxa et al,[29] 2015	Retrospective cohort (11.5)	34	ILT volume, thickness, and deposition (CT)	Aneurysm diameter	–	Significantly lower growth rate for AAAs with posterior vs anterior thrombus deposition (mean, −0.032 vs 0.336; $P = .035$); no difference in ILT volume (36 mL vs 35 mL; $P = .62$) or ILT thickness (14.4 mm vs 12.5 mm; $P = .57$) between high and low growth rate AAAs
Domonkos et al,[30] 2019	Retrospective cohort (24)	26	Relative ILT size (CTA)	Aneurysm diameter	–	Negative correlation between relative ILT size at baseline and aneurysm growth ($r = -0.32$; $P = .04$)
Zhu et al,[32] 2019	Prospective cohort (16)	41	ILT subtype, ILT area change, ILT volume change, baseline ILT volume, ILT thickness change (MRI)	Aneurysm diameter	–	Significantly higher growth rates in AAAs with bright ILT vs isointense ILT or no ILT (2.6 ± 2.5 mm/y vs 0.6 ± 1.3 mm/y vs 1.5 ± 1.6 mm/y; $P = .01$); threefold higher growth rate in AAAs with active ILT changes vs AAAs with stable ILT (3.6 ± 3.0 mm/y vs 1.2 ± 1.3 mm/y; $P = .008$); AAA growth not associated with ILT area ($r = 0.42$; $P = .06$) or ILT volume change ($r = 0.09$; $P = .70$), but a moderate association with ILT thickness changes ($r = 0.53$; $P = .02$) and baseline ILT volume ($r = 0.43$; $P = .05$)
Haller et al,[31] 2018	Retrospective case-control (ND)	51	ILT thickness, ILT% volume (CTA)	–	Confirmed by surgery	Significantly higher normalized ILT thickness and ILT% volume in small rAAAs vs large non-rAAAs (95% CI, 0.13-0.19 vs 0.10-0.13; $P < .01$; 95% CI, 59.6%-77.2% vs 50.2%-63.1%; $P = .02$) and small non-rAAAs (95% CI, 0.13-0.19 vs 0.08-0.13; $P < .01$; 95% CI, 59.6%-77.2% vs 42.9%-62.2%; $P = .02$)

AAA, Abdominal aortic aneurysm; *CI*, confidence interval; *CT*, computed tomography; *CTA*, computed tomography angiography; *FU*, follow-up; *ILT*, intraluminal thrombus; *IQR*, interquartile range; *MRI*, magnetic resonance imaging; *ND*, not determined; *rAAAs*, ruptured abdominal aortic aneurysms.

Intraluminal thrombus. Haller et al[31] performed a retrospective study including 51 AAA patients and divided them into four groups: small ruptured AAAs (n = 9), small nonruptured AAAs (n = 13), large ruptured AAAs (n = 14) and large nonruptured AAAs (n = 15). This study found a significantly higher ILT thickness and ILT volume for those with small ruptured AAAs compared with nonruptured AAAs (Table III). In contrast, another study including 108 patients found a lower ILT volume for ruptured AAAs compared with intact AAAs.[26]

Compliance. Two studies had investigated aneurysmal wall stiffness and distensibility in relation to rupture[37,38] (Table IV). One retrospective study (n = 132) found no differences in aneurysmal wall stiffness, determined by an ultrasonic echo-tracking system, in 11 ruptured AAAs compared with electively repaired AAAs.[37] Another study (n = 210) had included 28 ruptured AAAs, and found changes in the AAA elastic modulus, independently predictive of the time to rupture.[38]

Quality assessment

Most of the studies had scored at a moderate to low level of overall bias in the quality assessment (Supplementary Table II, online only). Three studies had scored an overall bias assessment of low during the quality assessment, indicating that no bias was found in these three studies. However, this was because the tool prescribed that when one category had scored higher than low, the overall score should be similar to that score. Most bias had occurred in the pre- and at-intervention domains of the ROBINS-I tool, especially in the bias due to confounding and bias in selection of participants, because not all the studies had corrected for, or reported, patient characteristics such as age, smoking, AAA diameter, and medical history. These quality assessments should be remembered when interpreting the results.

DISCUSSION

In the present review, we have provided an overview of the current evidence of the vascular characteristics of the aneurysmal wall and their relationship to growth and rupture in patients with an AAA, independently of the AAA diameter, who are currently not yet suitable for treatment using the current guidelines. First, some vascular characteristics of the aneurysm wall might well relate to AAA progression, with measures of the local abdominal aortic metabolism and calcification, in particular, related to AAA growth. Second, evidence regarding the relationships between the vascular characteristics and AAA rupture was not convincing owing to the conflicting results and small sample sizes. One measure that might predict AAA rupture is the aneurysmal wall metabolism, as assessed by USPIO uptake. However, the reported data only demonstrated a trend toward an association between USPIO uptake and AAA rupture, without statistically significant differences. Nevertheless, these data represent a finding that warrants further investigation. Therefore, a large prospective trial measuring USPIO uptake in AAAs and including larger numbers of ruptured AAAs during follow-up should be performed to better understand the predictive value of USPIO uptake. Within such studies, specific attention is required for potential between-individual and between-group differences to ultimately facilitate a more personalized approach in selecting the measures to predict the future risk of AAA rupture and growth.

Several measures of local aortic vascular health in relation to AAA growth were examined, and some measures might provide prognostic insight. In particular, measures related to local metabolism seemed to relate to AAA growth and USPIO uptake seemed to potentially relate to AAA rupture. The reported data have shown that AAA growth is more common in metabolically active AAAs than in metabolically inactive AAAs.[19-22] The mechanism of uptake varies for the different contrast agents.[34] ^{18}F-FDG uptake and USPIO uptake are regulated by macrophages that undergo classic activation (M1 macrophages) and macrophages with alternative activation (M2 macrophages), respectively. M1 macrophages are involved in the development of atherosclerosis, and M2 macrophages are involved in tissue remodeling and angiogenesis.[39] Since previous studies have suggested a potential role for USPIO uptake for prognostic insight regarding AAA growth, a potential role for M2 macrophages could be suggested and, thus, their contribution to tissue remodeling and angiogenesis in AAA development. Possibly, the activation of M2 macrophages represents an attempt within the pathophysiology of AAA development to improve the aneurysmal wall characteristics owing to the presence of a rapidly growing aneurysm. Nevertheless, both ^{18}F-FDG uptake and USPIO uptake are related to inflammation of the aneurysm wall, which is also involved in AAA progression.[40]

Another factor that might correlate to AAA growth is aneurysmal wall calcification, because some studies reported that the presence of calcification in the aneurysm wall seemed to have a protective effect on AAA growth.[23,25] During AAA growth, the aneurysm wall is subject to multiple pathologic processes, including the loss of vascular smooth muscle cells. Vascular smooth muscle cells regulate the vascular tone and vascular diameter but can also induce calcification when experiencing stress signals.[4] Although this suggests that faster AAA diameter growth might relate to greater calcification, previous studies have suggested the opposite.[23,25] This implies that calcified cells, perhaps owing to the limited deformation capacity of the cells, will stop or attenuate the other processes involved in AAA growth. The limited deformation capacity of the cells will also change the arterial compliance. Demer and Tintut[41] described the complex mechanisms behind vascular calcification and its link to several other components,

Table IV. Details of included studies of compliance as measuring type

Investigator	Study design (FU; months)	Sample size, No.	Measuring type (technique)	Outcome		Main findings of association with growth/rupture
				Growth	Rupture	
Wilson et al,[34] 1999	Prospective cohort (21)	60	Compliance using Ep and β parameters (ultrasonic echo-tracking)	Aneurysm diameter	–	No relationship between growth rate and Ep ($r = -0.09$) or β ($r = -0.13$) at end of follow-up
Vonk et al,[35] 2014	Prospective cohort (48)	7	Compliance, distensibility, E_{inc} (2D ultrasound elastography)	Aneurysm diameter	–	Higher relative increase in E_{inc} for fast growing AAAs (75%-700%) vs medium (25%-125%) and no growth (−10% to 100%) AAAs
Lorenzen et al,[36] 2021	Retrospective cohort (12)	326	Wall stiffness (ultrasound)	Aneurysm diameter	–	Baseline wall stiffness did not predict growth rate ($P = .32$); no correlation between change in wall stiffness and growth rate ($r = 0.053$; $P = .38$)
Sonesson et al,[37] 1999	Retrospective cohort (ND)	132	Wall stiffness (ultrasonic echo-tracking)	–	Confirmed by autopsy, emergency surgery, and clinically	No difference in aneurysmal wall stiffness in AAAs that subsequently ruptured vs electively repaired AAAs
Wilson et al,[38] 2003	Prospective cohort (19)	210	AAA distensibility using Ep and β parameters (ultrasonic echo-tracking)	–	Death certificate from NHS or hospital records	Significant association between Dmax ($P = .002$), change in Ep ($P = .011$), and DBP ($P = .004$) and time to rupture; no statistically significant difference in baseline Ep (2.61 N/m^2 vs 2.93 N/m^2; $P = .244$) or β (16.5 AU vs 19.8 AU; $P = .116$) between ruptured and non-ruptured AAAs

2D, Two-dimensional; *AAA,* abdominal aortic aneurysm; *β,* stiffness; *DBP,* diastolic blood pressure; *Dmax,* maximum anteroposterior abdominal aortic aneurysm diameter; E_{inc}, incremental Young's modulus; *Ep,* pressure strain elastic modulus; *FU,* follow-up; *ND,* not determined; *NHS,* National Health Service.

including vascular compliance. Calcification will increase arterial stiffness, which will decrease arterial compliance. However, compliance demonstrated no relation to AAA growth. Regarding the process and components of aortic calcification, the literature has demonstrated that aortic calcification is also linked to inflammation and metabolism.[41] Thus, aortic calcification represents a multifactorial state of the aortic wall, which could explain why calcification seems related to AAA growth and compliance alone does not.

The included studies did not present a strong convincing relationship between the several measurements of vascular characteristics in relation to AAA rupture risk, which could imply that rupture is not dependent only on aneurysmal wall characteristics. Rupture also depends on the strength and, thereby, the health state of the aneurysm wall. One measure that could, therefore, potentially be valuable in predicting rupture is the metabolism. However, the metabolism should be investigated in a study with larger numbers of ruptured AAAs. Nonetheless, such a study could be difficult to undertake, because the occurrence of rupture is unpredictable, and the current standard of care is to prevent ruptures. To explain the reason that the aneurysmal wall metabolism might have a potential relationship to AAA rupture, the mechanism of the studied contrast agents should be further clarified. When considering the contrast agents investigated in the different studies, both ^{18}F-FDG and USPIO had demonstrated a different distribution and pattern in uptake.[40] ^{18}F-FDG

uptake has been found more often in the AAA shoulder and USPIO in the main AAA body. Additionally, USPIO uptake is slower than that of ^{18}F-FDG.[42] This might indicate that USPIO is only measured when the inflammation process is advanced, because this will result in a sufficient concentration of inflammatory cells to cause a strong signal of USPIO uptake and, therefore, show a more convincing correlation with AAA growth and, potentially, with rupture than ^{18}F-FDG.

AAA rupture is not inextricably linked to growth but can also occur independently of AAA growth. One measure that demonstrated no conspicuous relationship with AAA growth was the ILT volume and thickness. This can be partly explained by the different parameters that were studied and the small sample sizes of the studies. This also applied to the evidence of ILT with regard to AAA rupture. However, a review by Schmitz-Rixen et al[43] indicated that ILT causes hypoxia in the aneurysm wall, which will lead to more inflammation, apoptosis of the vascular smooth muscle cells, and wall degradation and, thereby, activate the AAA metabolism,[44-46] which, in turn, could lead to AAA rupture. Therefore, the ILT and aortic wall metabolism could potentially provide a good description of the current state and strength of the aneurysm wall, which will also determine whether the aneurysm wall is prone to rupture.

Three limitations of the present review were the relatively low number of participants included in each study, the inconsistency in the end points (and associated methods), and the low event rates in the included studies. Because of these limitations, we refrained from performing a meta-analysis. These limitations should be considered when interpreting the results of our review and when designing future studies on this topic. Because the defined measures, in particular the metabolism, could be expensive or complicated to evaluate, it is important to know whether a selection bias of the participants narrowed the group who would benefit from these measures. However, the quality assessment found a low risk of bias, implying that the metabolic measures seem applicable to most AAA patients, except possibly for those with renal dysfunction, who were excluded from two studies. However, more research and larger trials are needed to confirm and define which AAA patients would benefit most from these measurements. Another limitation was the focus only on the local characteristics of the aneurysm wall. The presence of an AAA will influence the patient's health both locally and systemically.[47] Multiple studies have investigated the predictive value of surrogate measures, including biomechanical properties and biomarkers, on AAA growth and rupture.[48-51] A recent study by Yamaguchi et al[52] demonstrated that periaortic adipose tissue was an independent significant predictor for AAA progression. Additionally, flow-mediated dilation has been shown to have a weak, but significant, inversed correlation with future AAA progression.[53] A recent review of the literature by Siasos et al[54] highlighted the contribution of endothelial cells resulting from increased oxidative stress to AAA development. This emphasizes a potential role of measures of endothelial function and arterial stiffness in predicting AAA growth and rupture.

CONCLUSIONS

The current measures of local vascular characteristics of the aortic wall have the potential to predict AAA growth, especially measures of the metabolism and calcification. This implies that those measures best represent the processes in the aortic wall that lead to AAA progression. AAA rupture demonstrated no convincing relationship with one of the found measures. Although more work is needed, the metabolism could potentially be related to AAA rupture, because slightly more metabolic active AAAs were found among the ruptured AAAs than among the nonruptured AAAs. This emphasizes the role of the aortic wall characteristics in AAA progression and could, therefore, improve the prediction of AAA growth and rupture through the evaluation of these characteristics.

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AUTHOR CONTRIBUTIONS

Conception and design: JV, MM, DT
Analysis and interpretation: JV, MM, FV, MR, SH, DT
Data collection: JV, MM, FV
Writing the article: JV, MM
Critical revision of the article: JV, MM, FV, MR, SH, DT
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Additional material for this article may be found online at www.jvascsurg.org.

Supplementary Table I (online only). Search strategy for all databases

Database	Search terms
PubMed	((aortic aneurysm, abdominal[MeSH terms]) or (abdominal aort* aneurysm* [tw]) or (AAA[tw]) or (AAAs[tw]) or (aortic abdominal aneurysm[tw])) AND ((disease progression[MeSH terms]) or (aneurysm, ruptured[MeSH terms]) or (aortic rupture[MeSH terms]) or (prognosis[MeSH terms]) or (rupture risk[tw]) or (predict*[tw]) or (progress*[tw]) or (grow*[tw]) or (expan*[tw]) or (rupture*[tw])) AND ((vascular[tw]) or (wall[tw])) AND ((biomechanical phenomena[MeSH terms]) or (wall stress[tw]) or (shear stress[tw]) or (biomechanic*[tw]) or (compliance[MeSH]) or (stiff*[tw]) or (stress*[tw]) or (pulse wave velocity [tw]) or (wall tension[tw]) or (calcification[title/abstract]) or (inflammation[MeSH terms]) or (immune system phenomena[MeSH terms]) or (18F-FDG[tw]) or (inflammation[tw]) or (oxidative stress [MeSH terms]) or (reactive oxygen species[MeSH terms]) or (biomarkers [tw])) NOT ((endovascular procedures [MeSH terms]) (endovascular repair [tw]) or (treatment outcome[MeSH terms]) or (postoperative[title/ abstract]) or (surgery[title]) or (surgical repair[title]) or (EVAR[title]) or (graft [tw])) NOT ((animals[MeSH terms]) not (humans[MeSH terms])) not (mice [tw])
Web of Science	((abdominal aortic aneurysm AND (growth OR rupture)) AND (vascular OR wall) AND (biomechanical OR stress* OR compliance OR stiff* OR pulse wave velocity OR wall tension OR calcification OR inflammation OR 18F-FDG OR oxidative stress OR reactive oxygen species OR biomarkers) NOT (treatment OR therapy OR repair OR surgery OR mice OR animal OR models))

Supplementary Table II (online only). Risk of bias and quality assessment of included studies using ROBINS-I (risk of bias in nonrandomized studies of interventions) tool

	Risk of bias in pre- and at-intervention domains			Risk of bias in postintervention domains				
Investigator	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall assessment of bias
Siegel 1994	Low	Moderate	Low	NI	Low	Low	Low	Moderate
Sonesson 1999	Serious	Low	Low	NI	Low	Low	Low	Serious
Wilson 1999	Serious	Moderate	NI	NI	Low	Low	Low	Serious
Wilson 2003	Low	Moderate	Low	NI	Low	Low	Low	Moderate
Lindholt 2008	Moderate	Low	Low	NI	Low	Low	Low	Moderate
Speelman 2010	Low	Low	Low	NI	Low	Low	Low	Low
Kotze 2011	Moderate	Low	NI	NI	Moderate	Low	Low	Moderate
Richards 2011	Low	Low	Low	NI	Moderate	Low	Low	Moderate
Buijs 2013	Low	Low	Low	NI	Low	Moderate	Low	Moderate
Vonk 2014	Serious	NI	Serious	NI	Low	Low	Low	Serious
Hendy 2015	Low	Serious	Low	NI	Low	Low	Low	Serious
Metaxa 2015	Serious	Low	Low	NI	Low	Low	Low	Serious
Nakayama 2016	Low	Moderate	NI	NI	Low	Low	Low	Moderate
Forsythe 2018	Low	Low	Low	NI	Low	Low	Low	Low
Forsythe 2018	Low	Low	Low	NI	Low	Low	Low	Low
Haller 2018	Low	Low	Low	NI	Low	Serious	Low	Serious
Domonkos 2019	Serious	Moderate	Low	NI	Low	Moderate	Low	Serious
Zhu 2019	Moderate	Low	Low	NI	Moderate	Low	Low	Moderate
Kuzniar 2020	Moderate	Low	Low	NI	Low	Low	Low	Moderate
Lorenzen 2021	Low	Moderate	NI	NI	Low	Low	Low	Moderate

Critical, Critical risk of bias; *Low,* low risk of bias; *Moderate,* moderate risk of bias; *NI,* no information; *Serious,* serious risk of bias.